CLINICAL PROFILE AND LIPID ABNORMALITIES IN SUBCLINICAL HYPOTHYROIDISM

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CERTIFICATE

This is to certify that this dissertation titled "**CLINICAL PROFILE AND LIPID ABNORMALITIES IN SUBCLINICAL HYPOTHYROIDISM"** submitted by **DR.PRAMODH.K**. to the faculty of General Medicine, **The Tamil Nadu Dr. M.G.R. Medical University, Chennai** in partial fulfillment of the requirement for the award of MD degree branch I General Medicine, is a bonafide research work carried out by him under our direct supervision and guidance

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CONTENTS

INTRODUCTION

Subclinical hypothyroidism is defined as an elevated serum TSH level associated with normal total or free T_4 and T_3 values. The overall prevalence has been reported to range from 6 – 8% in women and 3% in men(up to 10% in women more than 60 years)[1]. Because of the frequency with which this condition is encountered, important questions have been raised regarding its clinical relevance and appropriate management.

One of the myths that surrounds subclinical hypothyroidism is that the laboratory profile of an elevated serum TSH and normal free thyroid hormone levels really represents "compensated hypothyroidism." The reasoning behind this idea is that, since the circulating levels of thyroid hormones are within the normal range with only the serum TSH being elevated, the affected subject is really euthyroid because the increased TSH is stimulating and driving the thyroid gland to produce normal thyroid hormone levels. Certainly, elevated serum TSH levels do stimulate even a diseased thyroid gland to produce and release more thyroid hormone. However, as long as the serum TSH level remains elevated, the thyroid hormone levels are not truly normal for that individual. The clearance kinetics of thyroid hormones and TSH from the circulation actually make such a conclusion inescapable. Because the half-life of T_4 is 7 days and that of T_3 is 1 day, the serum TSH, which has a half-life of less than 1 hour, would certainly be expected to return to

normal if thyroid hormone levels were, indeed, normal for that individual. An elevated TSH in an individual patient, thus, means that the circulating thyroid hormone concentrations are insufficient, with a few rare exceptions (TSH-secreting tumors, thyroid hormone resistance syndromes). Subclinical hypothyroidism represents mild thyroid failure and is a clinically important disorder that has adverse clinical consequences and that should be treated in most, if not all, cases [2.]

The etiologies of subclinical and overt hypothyroidism are identical. Chronic autoimmune thyroiditis (Hashimoto's disease) accounts for the majority of cases. Approximately 54% of patients with subclinical hypothyroidism have Hashimoto's disease with high serum concentrations of antithyroid microsomal or antithyroid peroxidase antibodies [3].

Subclinical hypothyroidism may increase the risk of coronary heart disease (CHD) by adversely affecting cardiovascular risk factors. Despite some conflicting results many studies have found that subjects with subclinical hypothyroidism have higher total cholesterol and low-density lipoprotein/cholesterol levels than euthyroid subjects. A cross-sectional study showed that subjects with subclinical hypothyroidism have increased C-reactive protein values. Subclinical hypothyroidism also has been associated with increased risk for atherosclerosis.

Another important concern is the progression of subclinical hypothyroidism to overt hypothyroidism during its natural history.Risk is

high if the TSH is more than 10 uIU/mL or thyroid peroxidase antibody is positive. In the Whickham survey the annual risk of women developing hypothyroidism was 4.3% per year if both an elevated serum TSH and anti-thyroid antibodies were found, 2.6% with elevated TSH alone, and 2.1% per year with positive anti-thyroid antibodies alone[4].In a recent prospective study on the spontaneous course of patients with subclinical hypothyroidism by Gerold Huber and team they concluded that risk factors for progression to overt hypothyroidism were base line TSH >12uIU/mL,decreased thyroid reserve and presence of thyroid peroxidase antibody [5].

This study mainly focuses on the clinical profile (symptoms and signs), etiology and lipid abnormalities of patients with subclinical hypothyroidism in our setting.

REVIEW OF LITERATURE

SUBCLINICAL HYPOTHYROIDISM

The term subclinical hypothyroidism was first introduced in the early 1970s coincident with the introduction of serum thyrotropin (TSH) measurements. This term eventually replaced other terms, such as preclinical myxedema, compensated euthyroidism, preclinical hypothyroidism, and decreased thyroid reserve.

Subclinical hypothyroidism is best defined as a high serum TSH concentration and normal serum free or total thyroxine (T4) and triiodothyronine (T3) concentrations associated with few or no symptoms or signs of hypothyroidism. Some investigators, especially those studying the neuropsychiatric aspects of hypothyroidism, also include patients who have high-normal basal serum TSH concentrations and supranormal serum TSH responses to thyrotropin-releasing hormone (TRH).

By definition, patients with subclinical hypothyroidism cannot be identified on the basis of symptoms and signs. Studies emphasize the difficulty in making the diagnosis of primary hypothyroidism using clinical symptoms alone; euthyroid subjects and patients with mild or overt hypothyroidism all had similar constellations of symptoms. It is important to note that, in Colorado study euthyroid subjects experienced a mean of 12.1% of all listed symptoms, overtly hypothyroid subjects had 16.6% of these symptoms and subjects with mild thyroid failure reported an intermediate 13.7% of the symptoms. This suggests a “dosage effect”

between levels of thyroid hormones and symptoms [6]. Consistent with these findings, a Swiss study involving 332 women with hypothyroidism reported that 24% of the 93 subjects with mild thyroid failure exhibited typical symptoms of hypothyroidism [7].

One of the myths that surround subclinical hypothyroidism is that the laboratory profile of an elevated serum TSH and normal free thyroid hormone levels really represents "compensated hypothyroidism." The reasoning behind this idea is that, since the circulating levels of thyroid hormones are within the normal range with only the serum TSH being elevated, the affected subject is really euthyroid because the increased TSH is stimulating and driving the thyroid gland to produce normal thyroid hormone levels. Certainly, elevated serum TSH levels do stimulate even a diseased thyroid gland to produce and release more thyroid hormone. However, as long as the serum TSH level remains elevated, the thyroid hormone levels are not truly normal for that individual. The clearance kinetics of thyroid hormones and TSH from the circulation actually makes such a conclusion inescapable. Because the half-life of T4 is 7 days and that of T3 is 1 day, the serum TSH, which has a half-life of less than 1 h, would certainly be expected to return to normal if thyroid hormone levels were, indeed, normal for that individual. An elevated TSH in an individual patient, thus, means that the circulating thyroid hormone concentrations are insufficient, with a few rare exceptions (TSH-secreting tumors, thyroid hormone resistance syndromes).

ETIOLOGY

The causes of subclinical hypothyroidism are the same as the causes of overt hypothyroidism. Most patients have chronic autoimmune thyroiditis, as defined by high serum concentrations of antithyroid peroxidase (anti-TPO) antibodies. In a Michigan outpatient practice, 54% of patients with subclinical hypothyroidism had chronic autoimmune thyroiditis, and in a community survey in Whickham, England, 67% of women and 40% of men with high serum TSH concentrations had high serum antibody values[3,8]. Destructive therapy for thyrotoxicosis caused by Graves' hyperthyroidism is another major cause of subclinical hypothyroidism, accounting for 39% of the cases in the Michigan study.

Among clinically euthyroid patients who have received radioiodine therapy for Graves' hyperthyroidism, at least half have high serum TSH concentrations, and in one survey, 65% of clinically euthyroid patients treated surgically for Graves' disease had high TSH concentrations[9,10].Several drugs may cause subclinical (or overt) hypothyroidism, including lithium carbonate, iodine, iodine-containing drugs such as amiodarone, and iodine-containing radiographic contrast agents. Smoking may exacerbate subclinical hypothyroidism and its metabolic consequences[11]. External radiation therapy to the neck also may cause subclinical hypothyroidism. Another important cause of subclinical hypothyroidism is inadequate thyroid hormone therapy for

overt hypothyroidism. In a community-based study (in Framingham, Massachusetts), 37% of older patients taking thyroid hormone preparations for hypothyroidism had high serum TSH concentrations[12]. Inadequate thyroid therapy may have been intentional in some patients because of coexisting heart disease, but more often it is caused by poor patient compliance or inadequate monitoring of therapy.

EPIDEMIOLOGY

Several population-based studies have defined the prevalence of subclinical hypothyroidism. In England (the Whickham Survey), the prevalence of serum TSH concentrations higher than 6 uIU/mL in the absence of overt hypothyroidism was 7.5% in women and 2.8% in men [8]. An age-dependent increase in serum TSH was found in women only when those with high serum antithyroid antibody concentrations were included in the analysis, and not all in men. In women aged over 75 years, the prevalence of subclinical hypothyroidism was 17.4%. In a similar study in Detroit, the prevalence of high serum TSH concentrations was 8.5% in women and 4.4% in men[13].

The higher prevalence of subclinical hypothyroidism in elderly patients was confirmed by data from the Framingham Study, in which the prevalence of minor elevations in serum TSH in patients aged over 60 years was 8.2% in men and 16.9% in women[14] and by a Dutch study in

which the prevalence of subclinical hypothyroidism in a group of women (mean age, 55 years) was 4%; the rate was 7.3% in the same group of women 10 years later. The prevalence of subclinical hypothyroidism may be lower in some elderly women; in an English study, the prevalence was 13.7% in women aged 60 to 69 years and 6.2% in women aged over 80 years[15].Subclinical hypothyroidism is more prevalent in areas of higher, as compared with lower, but not deficient, iodine intake. Among nursing home residents with a mean age of 80 years and similar prevalence of high serum anti-TPO antibody concentrations, the prevalence of subclinical hypothyroidism was 4.2% in relatively iodine-deficient northern Hungary; 10.4% in Slovakia, where iodinated salt prophylaxis had been mandated for 40 years; and 23.9% in Eastern Hungary, where iodine intake is high[16].Subclinical hypothyroidism is more prevalent in patients with Down's syndrome, type I diabetes mellitus, and probably other autoimmune diseases. In a survey of pregnant women in the United States, 2% had subclinical hypothyroidism, 58% of whom had high anti-TPO antibody values[17]. Smoking may worsen subclinical hypothyroidism and increase its peripheral effects. The effect of smoking was dose-dependent.

NATURAL HISTORY

A substantial proportion of patients with subclinical hypothyroidism eventually develop overt hypothyroidism. In a follow-up of persons from the original Whickham Survey, women who had high serum TSH and antithyroid antibody concentrations developed hypothyroidism at a rate of 4.3% yearly over 20 years, whereas women who had only high serum TSH concentrations or only high antibody concentrations developed hypothyroidism at an annual rate of 2.6% and 2.1%, respectively [4]. In a New Mexico study of asymptomatic ambulatory subjects with subclinical hypothyroidism older than 60 years, one third developed overt hypothyroidism during 4 years of follow-up; among them were all those whose initial serum TSH concentrations were higher than 20 uIU/mL and 80% of those whose serum anti-TPO antibody titers were 1:1600 or higher, but none with titers less than 1:1600. In an English study of persons with subclinical hypothyroidism followed for 1 year, 17.8% developed overt hypothyroidism, 5.5% had normal serum TSH concentrations, and 76.7% had persistent subclinical hypothyroidism[15]. The underlying cause of subclinical hypothyroidism also may predict progression to overt hypothyroidism. In one study, 53% of patients with subclinical hypothyroidism followed for 8 years became hypothyroid, and 47% continued to have subclinical hypothyroidism. The former group included all patients with autoimmune thyroid disease, prior radioiodine

therapy, high-dose external radiotherapy, and long-term lithium therapy, whereas the latter group included patients with thyroid or neck surgery for indications other than hyperthyroidism or external neck radiotherapy during childhood[18].

BIOLOGIC IMPORTANCE

The fundamental clinical question regarding patients with subclinical hypothyroidism is whether they require treatment with thyroid hormone. Based on the natural history of subclinical hypothyroidism alone, one can argue that treatment should be started to prevent the development of overt hypothyroidism. Additionally, goiter, if present, decreases in size in 77% of patients[19].

HYOPTHYROID SYMPTOMS AND PSYCOMETRIC OUTCOMES

Cooper et al. conducted double-blind trial in randomly assigned patients with subclinical hypothyroidism, including some patients with TSH >20 uIU/mL and symptoms such as dry skin, low energy and cold intolerance, to treatment with T4 or placebo for one year[20]. The dose of T4 was adjusted to normalize the serum TSH concentration. During treatment, one-half of the patients in the T4 group, but none in the placebo group, had fewer symptoms, as assessed by a standardized

hypothyroidism diagnostic index. Another trial was a double-blind cross-over study by Nyström et al. in which patients received either T4 (0.15 mg/day) or placebo, each for six months. The T4 dose was somewhat high; as a result, some patients may have had subclinical hyperthyroidism. Hypothyroid symptom scores and psychometric test results improved during the T4-treatment period, and about one-half of the patients felt better during this period, as compared with the placebo period[21].

Jaeschke et al. in their 10-month double-blind trial found a significant improvement in psychometric test scores, but no improvement in quality of life, during treatment with T4; some TSH values were as high as 32 uIU/mL[22]. In three trials serum lipid concentrations improved, as did hypothyroid symptom scores . In another trial in 40 women, in whom TSH values were between 5 and 10 uIU/mL, T4 had no beneficial effect on metabolic, serum lipid, or quality of life measures as compared with placebo[23]. A double blind randomized treatment trial of 69 patients with serum TSH between 3.5 and 10 uIU/mL failed to show any difference in cognitive function, emotional function, or hypothyroid symptoms scores on 17 different standardized questionnaires[24]. Thus, in two of three trials, psychometric test scores improved, and in three of six trials, hypothyroid symptoms improved, but no benefit was seen in the two trials of patients whose TSH values were under 10 uIU/mL.

CARDIOVASCULAR EFFECTS

Monzani et al. assessed only myocardial structure and contractility. Isovolumetric relaxation time and preejection/ejection ratio were increased and the cyclic variation index was decreased in patients with subclinical hypothyroidism. These alterations returned to normal with T4, but not with placebo. They also demonstrated an 11 percent improvement in carotid intima-media thickness with treatment of subclinical hypothyroidism[25] .

CARDIAC FUNCTION

Diastolic blood pressure was unchanged in one study, increased in two studies and mean arterial pressure fell after T4 treatment in another study. Some patients with subclinical hypothyroidism have diastolic dysfunction and increased peripheral vascular resistance, as noted in patients with overt hypothyroidism, and cardiac output increases and systemic vascular resistance decreases after T4 treatment[26,27,28]. Right ventricular systolic and diastolic functions were abnormal in one study and improved with T4 treatment. Systolic time intervals usually do not change , unless they were initially prolonged. The left ventricular ejection fraction at rest or during moderate exercise does not change, but may increase during maximal exercise. Myocardial contractility during maximal exercise also may increase[29].

CARDIOVASCULAR DISEASE

Subclinical hypothyroidism may also be associated with an increased risk of cardiovascular disease, coronary heart disease, and possibly, all-cause mortality . This was illustrated by the following studies: Flow-mediated dilatation, a measure of vascular endothelial response and an early marker for atherosclerosis, was impaired in a cross-sectional study of patients with subclinical hypothyroidism (mean TSH 8.85) compared with matched euthyroid controls.

The brachial-ankle pulse wave velocity, a parameter of arterial stiffening and a predictor of coronary atherosclerosis, was significantly increased in a cross-sectional study of patients with subclinical hypothyroidism (mean TSH 6.89). Central aortic pressure and arterial stiffness was increased in patients with subclinical hypothyroidism (mean TSH 8.8) and was reduced by treatment. Impaired endothelium-dependent vasodilatation was reversed by thyroxine treatment in a fourth report.Serum C-reactive protein and plasma asymmetric dimethylarginine (an endogenous nitric oxide synthase inhibitor) concentrations, appear to be high in patients with subclinical hypothyroidism, and are normalized by levothyroxine administration[30-33] . Platelet-activating factor (PAF) is a proinflammatory lipid mediator that has been implicated in atherogenesis. In plasma, PAF is inactivated by platelet-activating factor acetylhydrolase (PAF-AH). HDL-associated plasma PAF-AH activity is low in patients

with subclinical hypothyroidism (mean TSH 9.9), and increases to control values with levothyroxine therapy[34]. A number of observational studies have reported that, in general, older subjects with subclinical hypothyroidism are at increased risk for coronary heart disease. In one of these reports, the increased risk was seen in men, but not women , while in another, older subjects with subclinical hypothyroidism were at increased risk for developing heart failure, but not coronary heart disease(CHD)[35]. A meta-analysis of 14 observational studies of subclinical hypothyroidism calculated an overall increased risk of CHD (OR 1.65) . In summary, subclinical hypothyroidism may be associated with an increased risk of CHD. However, clinical trials are needed to assess whether thyroid hormone replacement reduces the risk of CHD in these patients. In contrast to the studies described above, the Cardiovascular Health Study of 3233 community-dwelling subjects over age 65 years reported that subclinical hypothyroidism was not associated with an increased risk of CHD, adverse cardiovascular outcomes, or mortality[36] . In addition, in a study of individuals over age 85 in the Netherlands followed for four years, those with untreated subclinical hypothyroidism actually had a lower rate of cardiovascular and all-cause mortality.

SERUM LIPIDS AND APOLIPOPROTEIN CONCENTRATIONS

Despite a few conflicting reports, many cross-sectional studies have found that serum total cholesterol concentrations in patients with subclinical hypothyroidism were similar to those of normal subjects; these concentrations did not consistently fall during T4 treatment. However, in the largest cross-sectional study to date (25,862 participants), subjects with modest elevations of serum TSH (between 5.1 and 10 uIU/L) had significantly higher mean total cholesterol concentrations than those who were euthyroid (223 versus 216 mg/dL [5.6 versus 5.8 mmol/L], $p<0.03$) [6]. It is not known whether this difference is clinically important with regard to cardiovascular risk.

There are no consistent changes in serum low-density-lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and apoprotein concentrations. In some studies patients with subclinical hypothyroidism had high serum LDL-cholesterol and low HDL-cholesterol concentrations[37,38,39], but the values were normal in other studies[41,42]. Serum apoprotein A1 concentrations were high in one study[42] and low in another[41] , serum lipoprotein (a) concentrations were high in another study[39], and serum apoprotein B concentrations were normal in some studies and high in two studies .In a randomized controlled trial in 66 women with subclinical hypothyroidism treated with T4, serum total and LDL cholesterol, and apoprotein B-100 concentrations decreased

significantly, whereas serum HDL cholesterol, triglyceride, and lipoprotein (a) concentrations did not change[43]. In two other studies, only serum total and LDL cholesterol concentrations decreased after T4 therapy.

In another study, apoprotein B levels fell after T4 therapy[41]. And in two non-randomized trials serum lipoprotein (a) concentrations were reduced by T4[44]. Further support for a mild increase in serum cholesterol in subclinical hypothyroidism comes from a pooled analysis of the published literature, which revealed that T4 therapy resulted in a small decrease in mean serum total cholesterol concentration of about 16 mg/dL (0.4mmol/L)[45]. In addition, a meta-analysis of 247 patients in 13 studies of subclinical hypothyroidism found that T4 therapy resulted in significant reductions in serum total cholesterol (8 mg/dL [0.2 mmol/L]) and serum LDL cholesterol (10 mg/dL [0.3 mmol/L]); the mean serum HDL cholesterol and triglyceride concentrations did not change. In this metaanalysis, reductions in serum cholesterol were only seen in patients with levels >240 mg/dL at baseline. Also, only those patients who had "subclinical hypothyroidism" based on inadequately treated overt hypothyroidism had statistically significant decreases in serum cholesterol[46].

NEUROPSYCHIATRIC FEATURES

Reports of an increased prevalence of subclinical hypothyroidism in patients with depression or bipolar affective disorders need careful assessment because of frequently inadequate control groups, coincident lithium therapy, and the inclusion of patients with normal serum TSH values whose thyroid abnormality is limited to either an increased response of serum TSH to TRH administration or high serum antithyroid antibody concentrations[47]. Nonetheless, several studies suggest an association of subclinical hypothyroidism with neuropsychiatric abnormalities. In one study, the prevalence of hypothyroidism was 14.8% in patients with neurotic depression and 2.3% in those with senile and multiinfarct dementia, as compared with 1.9% in patients with no psychiatric disorder. Patients with depression and subclinical hypothyroidism had a higher prevalence of associated panic disorder and a poorer response to antidepressant drug therapy than depressed euthyroid patients[48]. Randomly selected women with subclinical hypothyroidism who had formal psychiatric assessment before assessment of thyroid function had a higher lifetime frequency of depression than euthyroid women[49]. Women found to have subclinical hypothyroidism after presenting to a clinic for assessment of goiter had increased rates of free-flowing anxiety, somatic complaints, depressive features, and hysteria

compared with euthyroid women with goiter, and these abnormalities improved during treatment with T4[50].

In DeFaZhu et al. study (2006), functional MRI (fMRI))was used to measure brain functions by asking euthyroid subjects, hyperthyroid patients and subclinical hypothyroidism patients to perform the widely used digit n-back working memory task. After having been treated with L-thyroxine for ~6 months, the subclinical hypothyroidism patients were asked to do the same fMRI experiment. The hypothyroid and subclinical hypothyroidism patients scored significantly lower in the 2-back task than either the hyperthyroid patients or the euthyroid subjects ($P < 0.012$). The fMRI showed that a common frontoparietal network, including bilateral middle/inferior frontal gyri (M/IFG), bilateral dorsolateral prefrontal cortex (DLPFC), bilateral premotor areas (PreMA), the supplementary motor area/anterior cingulate cortex (SMA/ACC) and bilateral parietal areas (PA), was activated by the n-back task in all the subjects. Further quantitative analysis showed that the load effect of blood oxygen level-dependent (BOLD) response appeared in all the five regions of interest (ROIs) in the euthyroid and hyperthyroid subjects. In the pre-treatment subclinical hypothyroidism patients, however, the load effect of BOLD response was only found in the PA and PreMA, but not in other frontal cortex ROIs After an ~6 month treatment with LT4, the subclinical hypothyroidism patients exhibited the same load effects in all five ROIs

as the euthyroid subjects along with an improvement of performance in n-back task. These results suggest that working memory (but not other memory functions) is impaired in subclinical hypothyroidism patients. Both the memory performance and frontal executive functions were improved after an L-thyroxine-replacement treatment[51].

EFFECTS ON PREGNANCY AND FERTILITY

Undetected subclinical hypothyroidism during pregnancy may adversely affect the neuropsychological development and survival of the fetus and be associated with hypertension and toxemia, screening of pregnant women has been advocated in many countries. During pregnancy, thyroid hormone needs rise 45 % because of increases in thyroid hormone binding globulin[52]. It is critical that euthyroidism be maintained throughout pregnancy as shown by a recent study of women with a mean TSH level of only 13.2 uIU/mL at about 17 weeks of gestation. The offspring of these women had an average IQ score 4 points lower than euthyroid controls at age 7 to 9 years ($p=0.06$).Of those women not treated at all with L-T4 during the pregnancy, their children had an IQ deficit of 7 points ($P = .005$)[53]. In addition, data suggesting that subclinical hypothyroidism is associated with ovulatory dysfunction and infertility may make screening worthwhile in this population as well. Overt hypothyroidism may cause infertility from anovulation and

menorrhagia from estrogen breakthrough bleeding. Pregnancies that do occur during overt hypothyroidism are at increased risk of abortion, stillbirths, and prematurity. Those with elevations of antithyroid peroxidase and antithyroglobulin antibodies have a 10% rate of spontaneous abortion (double that of normal controls).Subclinical hypothyroidism can also produce menorrhagia, anovulatory cycles, and luteal phase dysfunction, all of which can lead to infertility.[54,55,56]. A study of 127 women with adult-onset amenorrhea showed that 7.5 percent of participants had abnormal prolactin levels and 4.2 percent had abnormal TSH levels[54] .

Abalovich et al. showed that it was not so much the diagnosis of overt *vs.* subclinical hypothyroidism that mattered in relation with pregnancy outcome but mainly the adequacy of levothyroxine treatment. The outcome of pregnancy was compared in 27 women with hypothyroidism already known before pregnancy and who received an adequate levothyroxine treatment with 24 women in whom levothyroxine treatment was not adequately adjusted during gestation and who, hence, did not reach euthyroidism. When the treatment was not adequate, pregnancy ended with abortion in 60 and 71% of overt and subclinical hypothyroid women, respectively, with an increased prevalence of preterm deliveries. Conversely, in hypothyroid pregnant women who

received an adequate treatment, the frequency of abortions was minimal and pregnancies carried to term without complications[57] .

SERUM TSH ELEVATIONS NOT ASSOCIATED WITH SUBCLINICAL HYPOTHYROIDISM

1. Recovery from nonthyroidal illness, at which time serum TSH may be transiently elevated for up to a week; these patients, therefore, should be reevaluated. Studies of subclinical hypothyroidism based on serum TSH measurements in hospitalized patients may be invalid because of failure to recognize this cause of high serum TSH values.
2. An occasional serum TSH determination may exceed the normal reference range because of a robust pulse of TSH secretion, especially at night, or because of assay variability.
3. Heterophilic antibodies, for example, in patients treated with monoclonal mouse antibody preparations, which interfere with TSH measurement.
4. Adrenal insufficiency
5. TSH-secreting pituitary adenomas, present as thyrotoxicosis.
6. Resistance to thyroid hormone; patient may be euthyroid or possibly thyrotoxic.
7. Metoclopramide or domperidone treatment

MANAGEMENT OF SUBCLINICAL HYPOTHYROIDISM

Subclinical hypothyroidism is common, especially among older women. Treatment may be indicated to prevent progression to overt hypothyroidism, especially in patients who have serum TSH concentrations greater than 10 uIU/mL and high serum anti-TPO antibody concentrations[58] . Progression to overt hypothyroidism occurs at a rate of 5 to 20 percent per year in patients with both mildly elevated TSH levels and antithyroid antibodies .Without treatment, only 5 percent of elevated serum thyrotropin levels will revert to normal values one year later in older persons. Treatment is also indicated if a goiter is present. The major immediate benefit of treatment is an improvement in symptoms and memory, a small reduction in serum total and LDL–cholesterol concentrations, and possible improvement in cardiac contractility.

Among patients with untreated subclinical hypothyroidism, there is no single level of serum TSH at which clinical action is always either indicated or contraindicated.As the TSH goes above 10 uIU/mL the basis for initiating treatment becomes more compelling .Clinical context is more important.There are no studies that demonstrate decreased mortality or morbidity with treatment.The potential risk of therapy are limited to the development of subclinical hyperthyroidism which may occur in 14 % to 15% cases.[58]

THOSE WITH TSH BETWEEN 4.5 AND 10 uIU/mL

Although early thyroxine treatment does not alter the natural history of disease it may prevent the symptoms and signs of overt disease in those who do progress.The available data do not confirm clear cut benefits for early therapy compared with treating when symptoms or overt hypothyroidism develops.There fore routine treatment of patients with TSH between 4.5 and 10 is not recommended, but thyroid function tests should be repeated at 6 to 12 months interval to monitor the improvement or worsening in TSH level.[58]

Some individuals with TSH between 4.5 and 10 may have symptoms compatible with hypothyroidism.Here the clinician may decide on a several month trial of levothyroxine,while monitoring for improvement in hypothyroid symptoms.Continuation of therapy should be predicted on clear symoptomatic benefit.[58]

THOSE WITH TSH MORE THAN 10 uIU/mL

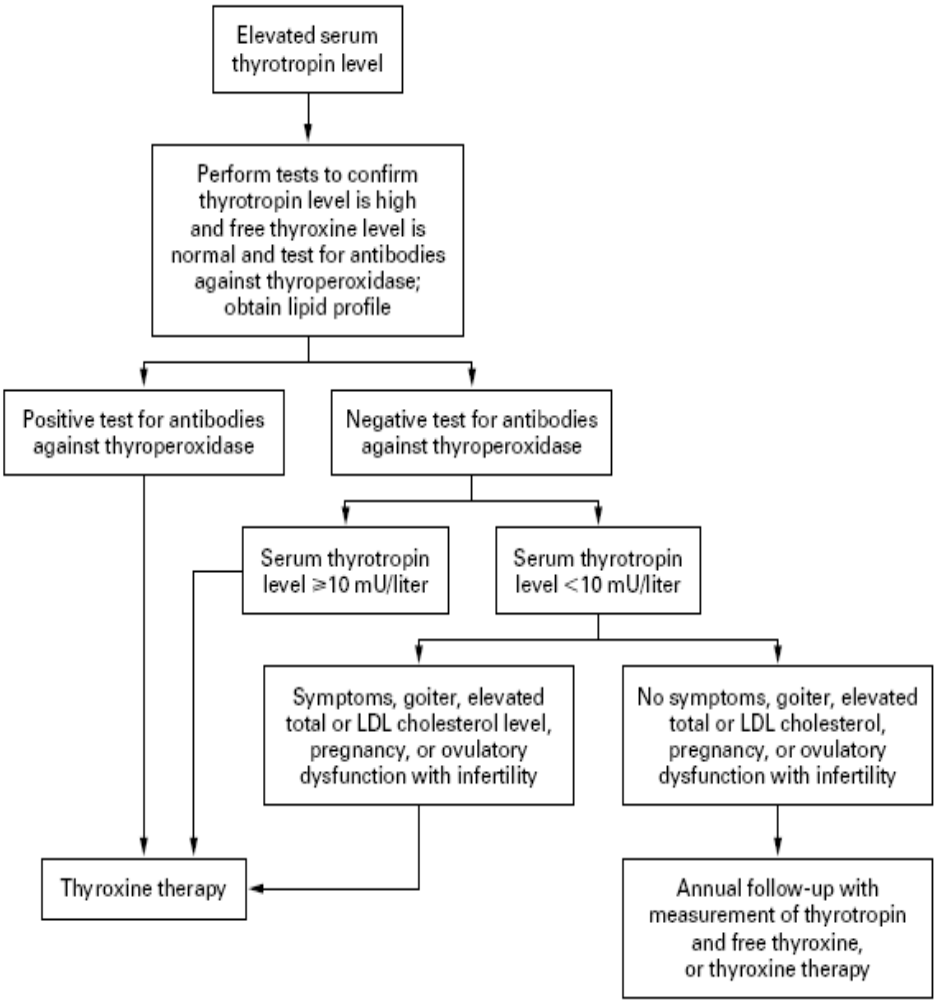
In this group levothyroxine therapy is reasonable. Treatment may potentially prevent the manifestations and consequences of hypothyroidism in those patients who do progress. Still, the evidence that therapy will reduce the total and LDL cholesterol level and improve symptoms in these patients is inconclusive.[58]

In general, treatment is strongly recommended in the following patients who have TSH levels higher than 10 uIU/L on repeated measurements, patients who have symptoms or signs (eg.goiter) associated with thyroid failure, patients who have convincing family history of thyroid disease, pregnant patients, patients who have a strong habit of tobacco use, or patients who have severe hyperlipidemia. An initial dose of thyroxine of 0.05 to 0.075 mg per day is usually sufficient to normalize the serum TSH level. Patients with coronary artery disease should receive lower initial doses (e.g., 0.0125 to 0.025 mg daily). Serum TSH levels should be measured four to six weeks after therapy is begun, after any change in the dose, and then annually, in order to achieve a serum TSH level between 0.5 and 3 mIU /mL once the levels become stable[4,15].

Arguments against treatment include the cost of therapy and the cost of monitoring therapy as well as the life-long commitment to daily medication in asymptomatic persons. In some patients, therapy may exacerbate angina pectoris or cardiac arrhythmia. If treatment is given, careful monitoring to avoid the adverse effects of subclinical thyrotoxicosis is mandatory. Although these concerns are not usually sufficient to counterbalance the benefits of therapy, recommendations are for a higher threshold for treating elderly patients with cardiovascular disease. If the patient is not treated, regular follow up is indicated.

ALGORITHAM TOR TREATMENT OF SUBCLINICAL HYPOTHYROIDISM

Fig 1



AIMS AND OBJECTIVES

1. To study the clinical profile of patients with subclinical hypothyroidism.
2. To identify the causes of subclinical hypothyroidism.
3. To identify the lipid profile abnormalities in patients with subclinical hypothyroidism.

MATERIALS AND METHODS

Source of the data

This was a hospital based cross sectional study conducted in Government Rajaji Hospital, Madurai. All adult patients who fitted the biochemical criteria for subclinical hypothyroidism were included in the study. None of the patients were part of a routine screening programme.

Design of study

Cross sectional, comparative study

Period of study

February 2008 to July 2008

Sample size

Cases 44

Controls 40

Ethical committee approval :obtained

Consent : Informed consent obtained

Financial support : Nil

Conflict of interest : Nil

Collaborating department:

Department of Endocrinology

Selection of study subjects

Newly diagnosed cases of subclinical hypothyroidism patients who fulfilled the inclusion and exclusion criteria were included in the study.

Inclusion criteria

1. All newly diagnosed cases of subclinical hypothyroidism(normal T3,T4&,fT4 with TSH more than 4.5uIU/mL)[58]

Exclusion criteria

1. Patients aged twelve or less.
2. Patients already on thyroxine
3. Patients who are not willing to give an informed consent.
4. Chronic renal failure,Chronic liver disease
5. Primary adrenal failure
6. Severe non thyroidal illness.
7. Patients who are on drugs like beta blockers,diuretics,steroids,OCP (causes dyslipidemia) and hypolipidemic drugs.
8. Known cases of diabetes mellitus were excluded while comparing lipid profile.

Selection of controls

Controls were taken for comparing the lipid profile of the cases. Healthy euthyroid (normal T3,T4,TSH) population were taken as controls.

Exclusion criteria for controls

1. Age less than 12 years.
2. Diabetes mellitus
3. Chronic renal failure
4. Chronic liver disease
5. Who were on drugs like beta blockers,diuretics,steroids,OCP & Lipid lowering drugs

Method of study

The patients in the study were group evaluated with a detailed clinical history, thorough clinical examination and relevant laboratory investigations. The diagnosis of subclinical hypothyroidism was made according to the diagnostic criteria mentioned above. The evaluation aimed to look for the symptoms and signs, probable etiology & lipid abnormalities.

Clinical data comprised of symptom analysis, thorough examination to identify signs, history of past medical illness and surgery, history of drug intake and type of salt used. Laboratory data consisted of blood sugar, blood urea, serum creatinine,T3, T4 ,TSH ,Ft4,TPO antibody and fasting lipid profile. Blood urea, sugar and serum creatinine were estimated using ERBA XL300 automated analyzer.T3 and T4 was measured by Competitive Chemi Luminescent Immuno Assay and TSH by Ultra Sensitive Sandwich Chemi Luminescent Immuno Assay. Anti

TPOantibody estimation was done in all cases by electrochemiluminescence assay.A value more than 34 IU/L is taken as positive. Fasting lipid profile was done with the ERBA XL300 autoanalyzer. Total cholesterol, Triglycerides and HDL were estimated and LDL was calculated by the Friedwald's equation :

$$\text{LDL Cholesterol} = \text{Total cholesterol} - \frac{\text{Triglycerides}}{5} - \text{HDL-C.}$$

Statistical Tools

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using **Epidemiological Information Package (EPI 2002).**

Using this software, range, frequencies, percentages, means, standard deviations, chi square and 'p' values were calculated. Kruskul Wallis chi-square test was used to test the significance of difference between quantitative variables. A 'p' value less than 0.05 is taken to denote significant relationship.

RESULTS

A. PROFILE OF STUDY CASES

Table 1: AGE DISTRIBUTION

Age in years	Study cases	
	No.	**%**
Upto 20 years	2	4.5
21-30	7	15.9
31-40	6	13.6
41-50	20	45.5
Above 50	9	20.5
Total	44	100
Range	13-68	
Mean	43.2	
S.D.	11.8	

A total of 44 newly diagnosed patients who fulfilled the inclusion criteria were studied.Their age ranged from 13 to 68 years and mean age was 43.2 years.Majority were in the age group 41 – 50 years.

Table - 2
SEX DISTRIBUTION

Sex	Study cases	
	No.	%
Male	3	6.8
Female	41	93.2
Total	44	100

Out of the 44 cases 41 (93.2%) were females and only 3 (6.8%) were males.

Table- 3

B M I

B M I	Study cases	
	No.	%
Lean (< 20)	10	22.7
Normal (20-25)	30	68.2
Obese (> 25)	4	9.1
Total	44	100
Range	20-26	
Mean	22.64	
S.D.	1.6	

Majority of the cases were having BMI in the range 20 –25 Kg/m^2.(30 cases/68.2%).

Table - 4

Symptoms

Symptoms	Present		Absent	
	No.	%	No.	%
Weight gain	26	59.1	18	40.9
Tiredness	28	63.6	16	36.4
Musculoskeletal	22	50	22	50
Neck swelling	14	31.8	30	68.2
Cold intolerance	17	38.6	27	61.4
Constipation	16	36.4	28	63.6
Voice changes	11	25	33	75
Depression	2	4.5	42	95.5
Infertility	3	6.8	41	93.2
Menorrhagia	8	18.2	36	81.8
Asymptomatic	-	-	44	100

Most common symptom in our study was excessive tiredness, which was present in 28 cases(63.6%).Next to tiredness most common complaint was a recent gain in weight, present in 26 cases(59.1%). Musculoskeletal complaints like myalgia and arthralgia was seen in 22 cases(50%). Other symptoms were neck swelling, cold intolerance,

constipation, hoarse voice and menorrhagia. We had 3 cases referred from Obstetrics and Gynaecology for evaluation of infertility and 2 cases from Psychiatry with clinical diagnosis of depression.None of our patients were entirely asymptomatic. Detaits of the symptoms are given in the table 4.

Table - 5

PAST HISTORY

Past Illness	Present		Absent	
	No.	%	No.	%
Hypertension	6	13.6	38	86.4
DM	4	9.1	40	90.9
IHD	4	9.1	40	90.9
Thyroidectomy	2	4.5	42	95.5
Hyperthyroidism	2	4.5	42	95.5

Six of our cases had history of hypertension and was on treatment. Four cases were diabetic. All are having T2DM.We also had four patients with Ischemic Heart Disease. Two cases had history of thyroidectomy for multinodular goiter. Two cases were on treatment for hyperthyroidism with carbimazole. Details of past illnesses are depicted in the table 5.

Table - 6
Salt Intake

Salt Intake	Study cases	
	No.	%
Iodised salt	36	81.8
Non iodised salt	8	18.2
Total	44	100

36 (81.8%) pateints in our study used to take iodised salt. Rest of the cases used to take non-iodised salt.

Table - 7

DRUG HISTORY

Drug	History of drug intake			
	Yes		No	
	No.	%	No.	%
Lithium	-	-	44	100
Amiodorone	1	2.3	43	97.7
Antithyroid drug	2	4.5	42	95.5
Radio iodine	-	-	44	100
Interferon	-	-	44	100

One patient with hypertension and ischemic heart disease was on Amiodarone for ventricular tachycardia for the past eight months. Two patients were on Carbimazole for hyperthyroidism. We didn't have any patients on Lithium, Radio Iodine or Interferon.

Table - 8

SIGNS ONCLINICAL EXAMINATION

Parameter	Study cases	
	No.	**%**
Pulse		
Normal	44	100
Bradycardia	-	-
B.P.		
Normal	38	86.4
Hypertension	6	13.6
Goitre		
Yes	24	54.5
No	20	45.4
Dry Skin		
Yes	18	40.9
No	26	59.1
Puffy Eyes		
Yes	9	20.5
No	35	79.5
Delayed relaxation of ankle jerk	6	13.6
Yes	38	86.4
No		

Most common sign was presence of goiter, which was seen in 24 cases(54.5%).Other signs were dry skin and puffiness of face and eyes present in 18(40.9%) and 9(20.5%) cases respectively.A delayed

relaxation of ankle jerk was present only in 6(13.6%) cases.None had bradycardia.

Table - 9

TSH DISTRIBUTION

TSH(uIU/mL)	No	%
< 10	8	18.2
10 - 20	33	75
> 20	3	6.8

33 cases (75%) were having TSH in the range 10 to 20. 8 patients(18.2%)had TSH between 5 and 10.Only 3 cases(6.8%) were having TSH above 20.

Table - 10

THYROID PEROXIDASE ANTIBODY(TPO Ab)

TPO Ab	No	%
Positive(>34IU/L)	26	56.1
Negative	18	40.9

26 cases (56.1%) had positive thyroid peroxidase antibody while 18 (40.9%) were negative for TPO Ab.

Table - 11

ETIOLOGY OF SUBCLINICAL HYOPOTHYROIDISM IN OUR STUDY.

ETIOLOGY	No	%
Auto immune thyroiditis	26	56.1
Post thyroidectomy	2	4.5
Antithyroid drugs	2	4.5
Amiodarone	1	2.3
Others	13	29.5

Most common cause of subclinical hypothyroidism in our study was Autoimmune thyroiditis,as suggested by the presence of thyroid peroxidase antibody,seen in 26 cases(56.1%).Other causes were post thyroidectomy and drug induced like antithyroid agent Carbimazole and antiarrythmic Amiodarone.No definite cause were found in 13 cases (2.5%). Details are depicted in table 11.

COMPARISON OF STUDY CASES AND CONTROL CASES

Table - 12

Age

Age group	Study cases		Control cases	
	No.	**%**	**No.**	**%**
Upto 20 years	2	4.5	2	5
21-30	7	15.9	5	12.5
31-40	6	13.6	5	12.5
41-50	20	45.5	16	40
Above 50	9	20.5	12	30
Total	44	100	40	100
Range	13-68		15-63	
Mean	43.2		44.8	
S.D.	11.8		12.2	
'p'	0.3697 Not Significant			

There was no significant difference in age distribution between the cases and the control group and hence they were comparable.

Table - 13

Sex

Sex	Study cases		Control cases	
	No.	**%**	**No.**	**%**
Male	3	6.8	-	0
Female	41	93.2	40	100
'p'	0.8524 Not Significant			

There was no significant difference in sex distribution between the cases and the control group and hence they were comparable

Table - 14

BMI

BMI	Study cases		Control cases	
	No.	**%**	**No.**	**%**
Lean (Upto 20)	10	22.7	14	35
Non Obese (20.1-25)	30	68.2	24	60
Obese (> 25)	4	9.1	2	5
Total	44	100	40	100
Range	20-26		19-27	
Mean	22.64		22.01	
S.D.	1.6		1.63	
'p'	0.0693 Not Significant			

There was no significant difference in BMI between the cases and the control group and hence they were comparable.

C : COMPARISON OF LIPID PROFILE

(*Only for case with normal fasting blood sugar)

Table - 15

Total Cholesterol

Total Cholesterol	Study cases (Subclinical hypothyroidism)		Control cases (Euthyroid)	
	No.	**%**	**No.**	**%**
Normal (≤ 200)	16	40	38	95
Borderline (201-239)	8	20	2	5
High (≥ 240)	16	40	-	-
Total	40*	100	40	100
Range	107-335		132-220	
Mean	213.3		165.8	
S.D.	59.6		19.4	
'p'	**0.0001 Significant**			

Hypercholesterolemia was present in 60% of subclinical hypothyroidism patients. The mean total cholesterol was 213.3 mg/dl in study cases and 165.8 mg/dl in control population. The difference was statistically significant . (p value 0.0001).

Table - 16

L D L

L D L	Study cases		Control cases	
	No.	**%**	**No.**	**%**
Normal (≤ 130)	19	47.5	38	95
Borderline (131-159)	2	5	2	5
High (≥ 160)	19	47.5	-	-
Total	40	100	40	100
Range	49-238		74-150	
Mean	138.6		109.4	
S.D.	48.7		18.1	
'p'	**0.005 Significant**			

LDL was elevated in 52.5% of subclinical hypothyroid group. 47.5% of cases had LDL more than 160mg/dl.The mean LDL in study cases was 138.6 mg/dl and 109.4 mg/dl in control group. The difference was statistically significant.(p value 0.005).

Table - 17

T G L

T G L	Study cases		Control cases	
	No.	**%**	**No.**	**%**
Normal (≤ 150)	29	72.5	38	95
Borderline (151-199)	6	15	1	2.5
High (≥ 200)	5	12.5	1	2.5
Total	40	100	40	100
Range	63-435		93-224	
Mean	143.6		126.4	
S.D.	81.1		23.7	
'p'	0.4853 Not Significant			

72.5% of the study cases were having triglycerides less than 150 mg/dl. The mean triglyceride level in subclinical hypothyroid group was 143.6 mg/dl and 126.4 mg/dl in control group. The difference was not statistically significant.(p value 0.4853).

Table - 18

HDL

HDL	Study cases		Control cases	
	No.	**%**	**No.**	**%**
Normal (≥ 40)	27	67.5	30	75
Low(< 40)	13	32.5	10	25
Total	40	100	40	100
Range	26-80		30-71	
Mean	46.08		49.93	
S.D.	13.77		11.37	
'p'	0.0813 Not Significant			

Majority of the study cases (67.5%) and control (75%) had HDL with in normal range. The mean HDL was 46.08 mg/dl in study group and 49.93 mg/dl in control group.The difference was not significant statistically.(p value 0.0813).

DISCUSSION

Subclinical hypothyroidism is defined as an elevated serum TSH with normal free T4. It is a more common condition than overt hypothyroidism. Many studies have shown that patients with subclinical hypothyroidism are not entirely asymptomatic, rather they do have many of the symptoms and signs of overt hypoythyroidism. In fact the term mild hypothyroidism or mild thyroid failure will be a more apt terminology for this condition [2].This study was done to find out the symptoms and signs, probable etiologies and lipid abnormalities in patients with subclinical hypoythyroidism, who presented in Government Rajaji Hospital, Madurai.

Among the 44 patients studied, the mean age was 43.2 years, range being 13 to 68 years. Majority of the patients (66%) were in the age group 41 – 68 years. Studies have shown that the incidence of subclinical hypothyroidism increases with age. The Colorado Thyroid Disease Prevalence Study had clearly demonstrated the increase in serum TSH with age [6](Fig 12). We had only 9 patients (20.5%) above the age group 50 years. This difference maybe due to the fact that those studies were community based screening studies done on large population. So screening in elderly population may be needed to detect more cases as larger studies have shown that majority of the patients are asymptomatic.

Fig 12

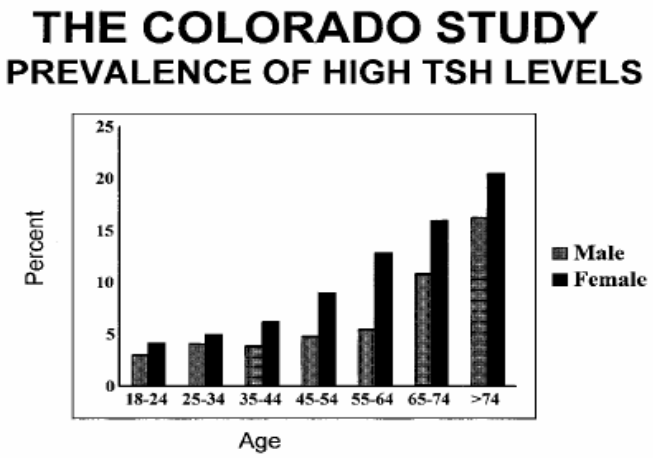


FIG. 1. The Colorado Thyroid Disease Prevalence Study (2). Shown are the age- and gender-specific prevalences of high serum TSH levels found during the screening of 25,862 Colorado state residents in 1995.

Studies have proven that the incidence of subclinical hypothyroidism is more in females. In our study also majority were females (93.2%). In a study on dyslipidemia in subclinical hypothyroidism by Bandyopadhay and co workers they also reported that 78% of their cases were females[59].

SYMPTOMS AND SIGNS OF SUBCLINICAL HYPOTHYROIDISM

Our study revealed that patients with subclinical hypothyroidism have symptoms that closely resemble that of overt hypothyroidism. Almost all patients had one or more symptoms mentioned in table 4. None of our cases were totally asymptomatic. This maybe due to the fact that ours is a hospital based study and we tend to miss those who are entirely asymptomatic unless screening has been done in high risk

population.Most common symptom was excessive tiredness (63.6%) followed by weight gain (59.1%) and musculoskeletal symptoms like myalgia and arthralgia (50%). Other symptoms noticed were neck swelling, constipation, cold intolerance, voice changes, depression, infertility and menorrhagia. The Colorado Thyroid Prevalence Study also revealed that subclinical hypothyroidism have symptoms similar to hypothyroidism. In their study 2,336 subjects who were identified as having mild thyroid failure, significantly reported more often having dry skin (28%; $P < 0.001$), poor memory (24%; $P < 0.001$), slow thinking (22%; $P < 0.001$), muscle weakness (22%; $P < 0.001$), fatigue 18%; $P < 0.01$), muscle cramps (17%; $P < 0.001$), cold intolerance (15%; $P < 0.001$), puffy eyes (12%; $P < 0.05$), constipation (8%;$P < 0.05$), and hoarseness (7%; $P < 0.05$) than did euthyroid subjects. It is important to note that, where as euthyroid subjects experienced a mean of 12.1% of all listed symptoms, overtly hypothyroid subjects had 16.6% of these symptoms ($P < 0.05$ *vs.* euthyroid group), and subjects with mild thyroid failure reported an intermediate 13.7% of the symptoms ($P < 0.05$ *vs.* euthyroid group). (Fig. 13). This suggests a "dosage effect" between levels of thyroid hormones and symptoms. [6]

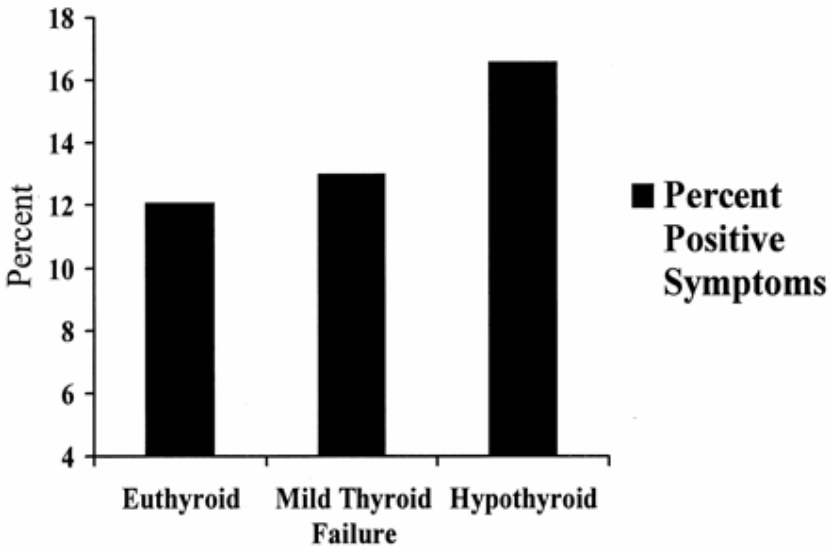


Fig 13. The Colorado Thyroid Disease Prevalence Study

In a study on clinico biochemical spectrum of hypothyroidism by Sampath et al generalized weakness and weight gain were the most common symptoms reported by both subclinical hypothyroid patients and overt hypothyroid patients[60].

Most common sign in our study was presence of goiter. Other signs were dry skin, puffiness of eyes and delayed relaxation of ankle jerk (table 8).

Except for goiter, signs in our study were similar to the observations in the Colorado study and the work by Sampath et al. It may be noted that goiter has been shown by other studies to be twice as prevalent among patients with subclinical hypothyroidism as in the general population[61].

In our study we had two patients with depression referred from psychiatry department. Neither of them were on any drugs. In a study by Haggerty et al the lifetime frequency of depression was significantly higher in the subjects who met the criteria for subclinical hypothyroidism (56%), than in those who did not (20%), suggesting that subclinical hypothyroidism may lower the threshold for the occurrence of depression[49]. In another study by Sampath et al 109 patients with depression were tested for thyroid dysfunction. 42.2% of them had subclinical hypothyroidism and 3.6% had overt hypothyroidism[60]. So all patients with depression should have a thyroid function test.

The prevalence of subclinical hypothyroidism has been reported to be 0.7–2.3% in a large series of unselected infertile women by Shalev et al 1994 & Lincoln et al 1999[62,63]. In our study 6.8% cases were having primary infertility. Some patients with infertility and menstrual irregularities may have underlying chronic thyroiditis in conjunction with subclinical or clinical hypothyroidism. Typically these patients seek medical attention because of infertility or a previous miscarriage, rather than hypothyroidism[64]. In the study by Sampath et al among 105 patients with primary infertility three patients were hypothyroid and 39 (37.1%) patients had subclinical hypothyroidism (total of 40% had thyroid dysfunction in the form of subclinical or overt hypothyroidism)[60].

SUBCLINICAL HYPOTHYROIDISM AND IODINE INTAKE

Another important observation of our study was significant incidence of goiter and subclinical hypothyroidism in a population where majority were on iodised salts (81.8% of total study group) .

Iodine is essential for thyroid function. Thyroid disorders related to iodine deficiency have decreased progressively with iodine prophylaxis and the increased overall iodine intake.

Acute excess iodine ingestion has long been known to result in a transient decrease in iodine organification, termed the acute Wolff-Chaikoff effect .With sustained excess iodine exposure, however, most individuals' thyroid glands escape from this acute Wolff-Chaikoff effect despite the exposure and resume synthesis of normal amounts of T_4 and T_3. The mechanism responsible for this escape or adaptation to the iodine load probably involves a decrease in the Na^+/I^- symporter protein, resulting in a decrease in thyroid iodide content .In some individuals this escape phenomenon does not occur, and those patients develop iodine-induced hypothyroidism. Such hypothyroidism generally is reversible when the source of excess iodine exposure is removed.

Another adverse effect resulting from iodine prophylaxis may be the induction of thyroid autoimmunity. Iodine and iodine containing drugs can precipitate autoimmune thyroiditis in susceptible populations[65]. Most common cause of subclinical hypothyroidism in our study was also

autoimmune thyroiditis as suggested by TPO antibodies.(table 11). A cross-sectional survey of 102 Peace Corps volunteers in Niger, West Africa, in 1998 had demonstrated a high rate of thyroid dysfunction and goiter attributable to excess iodine from their water filters. The study showed that during prolonged excess iodine exposure, there was a marked increase in serum total iodine concentrations. And the prevalence of goiter, elevated serum TSH values, and elevated serum thyroid peroxidase antibody values also increased. The prevalence of all abnormalities decreased after removal of excess iodine from the drinking water system[66]. Thyroid autoimmune diseases are complex, polygenic afflictions, the penetrance of which is heavily dependent on various environmental influences. In general, iodine deficiency attenuates, while iodine excess accelerates autoimmune thyroiditis in autoimmune prone individuals[67] .

In the present scenario of the post–iodination status in India, the high prevalence of subclinical hypothyroidism is significant as similar findings were reported from other countries, stating subclinical hypothyroidism is more prevalent and marked in subjects consuming excessive amounts of iodine. Excessive iodine intake should be considered an etiology of subclinical hypothyroidism in addition to chronic thyroiditis in these areas.

ETIOLOGY

Our study evaluated the causes for subclinical hypothyroidism. Most important aetiology found was autoimmune thyroiditis. Other causes were post thyroidectomy and drug induced like antithyroid agent Carbimazole and antiarrythmic like Amiodarone. No definite cause was found in 13 cases (29.5%).

Autoimmune thyroidits was diagnosed by doing anti TPO assay. 56.1% patients had positive thyroid peroxidase antibody test. This result was similar to the study by Shruti Mohanty and team where 45 out of 61 subclinical hypothyroid cases had TPO antibodies suggesting autoimmune thyroiditis as the cause[68]. Published literature states that the most common cause of subclinical hypothyroidism is autoimmune thyroiditis (Hashimoto's disease)[64]. Progression to overt hypothyroidism is reported to vary from 3 to 20%, the risks being greater in those patients with TSH more than 10 uIU/mL or thyroid antibodies (or both). Hence it is recommended that anti- TPO measurement should be an integral part of the investigation in subclinical hypothyroidism.

In a study by Ian Louis Ross about thyroid dysfunction in patients on amiodarone, he found that hypothyroidism was the common abnormality and subclinical hypothyroidism was present in 13% of cases[69]. Some studies indicate that the incidence of thyroid dysfunction with amiodarone varies with the dietary iodine intake in the population.

Amiodarone Induced Thyrotoxicosis occurs more frequently in geographical areas with low iodine intake, whereas Amiodarone Induced Hypothyroidism is more frequent in iodine-replete areas. Our study population was from an iodine-replete area and amiodarone was indeed found to be a cause for subclinical hypothyroidism.

SUBCLINICAL HYPOTHYROIDISM AND DYSLIPIDEMIA

While the association between overt hypothyroidism and alteration in lipid profile is an undisputed fact, the situation is less clear when subclinical hypothyroidism is concerned. The relationship between subclinical hypothyroidism and reversibly elevated lipid levels has been widely investigated, but the results remain highly controversial.

In this study, there was found to be a significant increase in the total cholesterol and LDL levels in study cases when compared with euthyroid controls, but the variation in HDL and triglycerides were not significant.

This result was similar to the observations made in The Colorado Thyroid Prevalence Study where they found statistically significant elevation in total cholesterol and LDL in subclinical hypothyroid cases compared with euthyroid controls[6]. Another study done in India by Guptha and Sinha also demonstrated a significant elevation in serum cholesterol in subclinical hypothyroid cases when compared with euthyroid controls[70]. Same results were obtained in the study by

Walsh J P & colleagues[71]. A recent meta-analysis of the effect of treatment with thyroxine on lipid profile in mild thyroid failure cases by Mark D. Danese and colleagues has demonstrated a mean reduction in the total cholesterol level of 7.9 mg per deciliter (0.2 mmol per liter) and in the LDL cholesterol level of 10 mg per deciliter (0.26 mmol per liter). Changes in high-density lipoprotein (HDL) cholesterol were heterogeneous among the studies and were not statistically significant[46].

A cross sectional study on the lipid abnormalities in subclinical hypothyroidism by Z Efstathiadou and coworkers demonstrated significant elevation of total cholesterol,LDL-C,apolipoprotein B and Lp(a) in subclinical hypothyroidism patients compared with euthyroid (p value<0.05).They also demonstrated that changes in triglycerides and HDL-C was not significant[72].These results were similar to our study.In conclusion lipid abnormalities are relatively common in subclinical hypothyroidism.Several randomized controled trials have shown that treatment of subclinical hypothyroidism with thyroxine may have a favourable effect on the lipid profile by decreasing total cholesterol and LDL-C.

These observations reinforces the need to screen for thyroid dysfunction in people with dyslipidemia, as this may be a reversible cause, amenable to thyroxine replacement.

72.7% of our patients (32/44) had indications as per the current recommendations for initiating thyroxine therapy. Indications for thyroxine were TSH more than 10 uIU/mL, TPO antibody positivity, presence of goiter, elevated total cholesterol or LDL and infertility. Majority had more than one indication as per the recommendations. Therapy was initiated with 50 mcg of thyroxine once daily. Untreated patients were adviced repeat thyroid function test after six months. Treated patients were also advised long term follow up to assess the benefit of therapy as well as to prevent therapy related complications like devolopment of iatrogenic hyperthyroidism.

CONCLUSIONS

1. Incidence of subclinical hypothyroidism is more in females as expected.
2. Being a hospital based study almost all of our patients are symptomatic.We tend to miss those who are entirely asymptomatic. Screening programmes in high risk population may help to detect those cases.
3. Most common symptom is excessive tiredness and most common sign is goiter.
4. Majority of our patients are at high risk for progressing to overt hypothyroidism (TSH>10 uIU/mL & TPO positivity).
5. 75% of patients has TSH between 10 and 20 uIU/mL.
6. TPO antibody is positive in 56.1% of cases.
7. Auto immune thyroiditis is the most common cause of subclinical hypothyroidism in our study.
8. Occurence of goiter and autoimmune thyroiditis in an iodine sufficient population supports the hypothesis that iodine may initiate or exacerbate thyroid autoimmunity in susceptible persons.
9. Subclinical hypothyroidism may be associated with infertility and depression. Screening may be beneficial in such cases.
10. Lipid abnormalities are seen in subclinical hypothyroidism patients in the form of significant elevation of total cholesterol and LDL

while changes in HDL and triglycerides are not significant. Follow up of treated patients are necessary to assess the benefit of thyoxine in reverting the lipid abnormalities.

11. 72.7% of cases received treatment with thyroxine in our study. Majority of them has multiple indications for starting treatment as per the current recommendations like TSH more than 10 uIU/mL, TPO Antibody positivity, goiter, hypothyroid symptoms, dyslipidemia and infertility. Follow up is needed to assess the benefit of treatment.

SUMMARY

Subclinical hypothyroidism is defined as an elevated serum TSH level associated with normal total or free T4 and T3 levels. This is a much more common disorder than overt hypothyroidism.

This study was done to find out the symptoms and signs, probable etiologies and lipid abnormalities in patients with subclinical hypoythyroidism, who presented in Government Rajaji Hospital, Madurai.

After institutional ethical clearance, with an informed consent and with inclusion and exclusion criteria 44 cases of subclinical hypothyroidism were included in the study and were evaluated on clinical and biochemical aspects. For comparing the lipid profile, 40 euthyroid controls who were age, sex and BMI matched and fitted the inclusion and exclusion criteria were selected. The data was entered in the master sheet and analysed statistically.

Subclinical hypothyroidism was more common in females in our study. Being a hospital based study majority of our patients were having symptoms.We tend to miss those patients who are entirely asymptomatic. Screening of high risk populations may help to detect those cases. The most common symptom was excessive tiredness, weight gain and musculoskeletal complaints like myalgia and arthralgia. Goiter was the most common sign on physical examination. Most of our patients were having risk factors for progression to overt hypothyroidism like baseline

TSH > 10 uIU/mL and presence of TPO antibodies. Auto immune thyroiditis was identified as the most common cause of subclinical hypothyroidism in our study. Diagnosis was made by the presence of TPO antibodies. The observation of increased incidence of autoimmune thyroiditis in an iodine sufficient population is supporting the hypothesis that thyroid autoimmunity can be initiated by iodine in susceptible individuals. Depression and infertility may be associated with subclinical hypothyroidism and screening of such individuals may be useful. Compared with euthyroid controls, cases with subclinical hypothyroidism had significantly elevated total cholesterol and LDL-C levels. Majority of our patients had multiple indications for starting thyroxine as per the current recommendations.

It is very important to follow up the treated cases for assessing the benefit of thyroxine on different aspects of subclinical hypothyroidism namely the effect on symptoms, reduction in goiter size, improvement in lipid abnormalities and also to avoid over treatment as . Untreated cases has to be followed up for evidence of progression of disease.

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APPENDIX I

PROFORMA

STUDY ON CLINICAL PROFILE AND LIPID ABNORMALITIES IN SUBCLINICAL HYPOTHYROIDISM

Name Age Sex

Address Occupation

Phone

FINAL DIAGNOSIS

DIAGNOSTIC CRITERIA

Elevated TSH level(>4.5uIU/mL) with normal total or free T4 & T3 values

SYMPTOMS

Asymptomatic	Tiredness
Weightgain	Neck swelling
Muscle weakness	Depression
Muscle cramps	Cold intolerance
Myalgia,arthralhia	Anorexia
Constipation	Infertility

PAST HISTORY

CAD	Dyslipidemia	DM
Hypertension	Autoimmune diseases	CRF
TB	Thyroidectomy	Asthma
Severe nonthyroidal Illness	Adrenal Failure	

Menstrual History: Menorrhagia Menopause

Obstetric History : Infertility,miscarriages

Treatment history: H/o:Drugs (Thyroxin / Lithium / Amiadarone,antithyroid,Interferon),Radio iodine ,H/o neck Radiation .

Salt intake : Iodised / non iodised

GENERAL EXAMINATION

Built	Nourishment		BMI	Pallor
Icterus	Cyanosis	Clubbing	Edema	Lymphadenopathy
Pulse rate	BP	RR	Temp	Peripheral pulses

THYROID

Diffuse Nodular Thyroidectomy scar

RESPIRATORY SYSTEM

Pleural Effusion Other findings

CVS

Cardiomegaly Murmur

MUSCULO SKELETAL

Arthralgia-

Myalgia

Stiffness Carpel tunnel syndrome Muscle weakness

NERVOUS SYSTEM

Neuropathy Seizures

Cerebellar signs Delayed Relaxation of DTR

ALIMENTARY SYSTEM

OTHERS

Periorbital Puffiness Dry, Coarse Skin Ichthyosis

Macroglossia Loss of Hair

INVESTIGATIONS

Urine - Albumin , Sugar , Casts , RBC

FBS, PPBS, Blood Urea , Serum Creatinine

TFT- T3 T4,fT4 TSH

FLP- T. CHOLESTEROL LDL HDL TG

Immunological test

Anti TPO Antibodies

APPENDIX II
MASTER CHART CASES

Sl No	age	sex	wt.gain	tiredness	musculoskeletal	neck swelling	cold intolerance	constipation
1	39	1	2	1	1	2	1	2
2	26	1	1	1	1	1	2	2
3	44	1	1	1	2	2	2	2
1	13	1	2	2	1	1	2	2
5	50	1	1	2	2	2	1	2
6	28	1	1	2	1	1	1	2
7	48	1	1	1	2	2	2	1
8	47	1	1	1	2	2	2	1
9	53	1	2	1	2	2	2	1
10	33	1	1	2	1	1	1	2
11	50	1	1	1	2	2	1	2
12	54	1	1	1	2	2	1	2
13	22	1	1	2	2	1	2	2
14	42	1	2	1	2	2	1	1
15	45	1	1	1	2	2	2	2
2	52	1	1	1	1	2	2	2
17	50	1	2	2	1	2	2	1
18	39	1	1	1	2	1	2	1
19	58	1	2	2	1	2	2	1
20	49	1	1	2	2	1	1	2
21	44	1	1	1	1	2	2	2
22	38	1	1	1	2	2	1	1
23	30	1	2	1	1	1	1	2
24	48	1	2	1	1	2	2	2
25	39	1	1	2	2	2	1	2
26	46	1	2	1	1	2	2	1
27	49	1	2	1	2	2	2	1
28	34	1	2	1	1	1	1	2
29	49	2	1	1	2	2	2	2
30	55	1	1	2	1	2	2	2
31	44	1	2	2	2	2	1	2
32	24	1	1	1	1	1	2	2
33	68	2	2	1	1	1	2	1
34	58	1	2	2	1	2	1	2
35	47	1	2	2	1	2	1	2
36	60	1	2	2	1	2	2	1
37	54	1	1	1	2	2	2	1
38	49	2	2	1	1	2	2	2
39	20	1	1	2	2	1	2	1
40	48	1	1	1	2	2	1	2
41	50	1	2	2	1	2	1	1
42	30	1	1	1	2	2	2	2
43	28	1	1	1	2	1	2	1
44	45	1	1	1	1	1	2	2

voice change	depression	infertility	menorrhagia	asymptomatic	salt intake	Hyper tension	DM	IHD
2	2	2	2	2	1	2	2	2
2	2	2	1	2	1	2	2	2
1	2	2	2	2	1	2	2	2
2	2	2	2	2	1	2	2	2
2	2	2	2	2	1	2	2	2
2	2	2	1	2	1	2	2	2
1	2	2	2	2	1	2	2	2
2	2	2	2	2	1	2	2	2
2	2	2	2	2	1	2	2	2
2	2	1	1	2	2	2	2	2
2	2	2	2	2	1	2	2	2
2	2	2	2	2	1	2	2	2
2	2	2	1	2	1	2	2	2
2	2	2	2	2	1	2	2	2
2	2	2	2	2	1	2	2	2
1	2	2	2	2	1	2	2	2
2	2	2	2	2	2	2	2	2
1	2	2	2	2	1	2	2	2
2	2	2	2	2	1	1	2	2
2	2	2	2	2	1	2	2	2
1	2	2	2	2	1	2	2	2
2	2	2	2	2	1	2	2	2
2	2	1	1	2	2	2	2	2
2	2	2	2	2	2	2	2	2
2	1	2	2	2	1	2	2	2
1	2	2	2	2	1	2	2	2
2	2	2	2	2	1	2	2	2
2	2	1	2	2	1	2	2	2
1	2	2	2	2	2	1	1	2
2	2	2	2	2	2	2	2	2
2	2	2	2	2	1	2	2	2
2	2	2	2	2	1	2	2	2
2	2	2	2	2	1	1	1	1
2	2	2	2	2	1	1	1	1
2	2	2	2	2	2	2	2	2
2	2	2	2	2	1	1	2	1
1	2	2	2	2	1	2	2	2
1	2	2	2	2	1	1	1	1
2	2	2	1	2	1	2	2	2
1	1	2	2	2	2	2	2	2
2	2	2	2	2	1	2	2	2
1	2	2	1	2	1	2	2	2
2	2	2	1	2	1	2	2	2
2	2	2	2	2	1	2	2	2

Hyper thyroidism	Thyroid dectomy	Lithium	Amiodarone	Antithyroid drugs	RAI	Interferon	pulse	BP
2	2	2	2	2	2	2	1	1
2	2	2	2	2	2	2	1	1
2	2	2	2	2	2	2	1	1
2	2	2	2	2	2	2	1	1
2	2	2	2	2	2	2	1	1
2	2	2	2	2	2	2	1	1
2	2	2	2	2	2	2	1	1
2	2	2	2	2	2	2	1	1
2	2	2	2	2	2	2	1	1
2	2	2	2	2	2	2	1	1
2	2	2	2	2	2	2	1	1
1	2	2	2	1	2	2	1	1
2	2	2	2	2	2	2	1	1
2	2	2	2	2	2	2	1	1
2	1	2	2	2	2	2	1	1
2	2	2	2	2	2	2	1	1
1	2	2	2	1	2	2	1	1
2	2	2	2	2	2	2	1	1
2	2	2	2	2	2	2	1	2
2	2	2	2	2	2	2	1	1
2	2	2	2	2	2	2	1	1
2	1	2	2	2	2	2	1	1
2	2	2	2	2	2	2	1	1
2	2	2	2	2	2	2	1	1
2	2	2	2	2	2	2	1	1
2	2	2	2	2	2	2	1	1
2	2	2	2	2	2	2	1	1
2	2	2	2	2	2	2	1	2
2	2	2	2	2	2	2	1	1
2	2	2	2	2	2	2	1	1
2	2	2	2	2	2	2	1	1
2	2	2	1	2	2	2	1	2
2	2	2	2	2	2	2	1	2
2	2	2	2	2	2	2	1	1
2	2	2	2	2	2	2	1	2
2	2	2	2	2	2	2	1	1
2	2	2	2	2	2	2	1	2
2	2	2	2	2	2	2	1	1
2	2	2	2	2	2	2	1	1
2	2	2	2	2	2	2	1	1
2	2	2	2	2	2	2	1	1
2	2	2	2	2	2	2	1	1
2	2	2	2	2	2	2	1	1

goitre	dry skin	puffy eyes	DRAJ	BMI	FBS	TSH	FT4	TPO Ab	TC	TG	LDL	HDL	LT4 STARTED
2	1	2	2	20	1	24.6	1.23	1	185	100	120	45	1
1	2	1	2	22	1	17.7	2.2	1	260	185	180	43	1
1	1	2	2	21	1	14.73	1.4	1	255	90	191	46	1
1	2	2	2	20	1	14.07	1.9	2	156	80	102	38	1
2	1	1	2	25	1	7.19	0.98	2	120	66	67	40	2
1	1	2	1	22	1	16.6	1.3	1	113	92	49	46	1
2	1	2	2	22	1	18.76	1.76	1	233	122	167	42	1
1	2	1	2	23	1	6.98	2	2	146	78	98	32	2
2	2	2	2	21	1	8.7	2.4	2	180	142	106	46	2
1	2	2	2	22	1	14	2.3	1	310	119	238	48	1
2	1	2	1	23	1	7.8	1.7	2	107	72	56	37	2
2	1	2	1	24	1	10.2	1.5	2	126	98	80	26	2
1	2	2	2	23	1	19.8	1.32	1	137	63	90	35	1
2	1	2	2	25	1	13.2	2.23	1	262	284	149	56	1
2	2	2	2	22	1	14.3	1.65	2	160	110	101	37	1
2	1	1	2	21	1	10.8	1.4	1	280	122	208	48	1
2	2	2	2	23	1	7.6	1.6	2	204	106	127	56	2
1	2	2	2	21	1	12.9	1.73	1	241	96	188	34	1
2	2	2	2	26	1	10	0.93	2	222	92	154	50	2
1	1	2	2	23	1	11.5	1.65	1	246	82	189	41	1
1	2	2	2	22	1	13.6	1.8	1	246	435	131	28	1
2	2	2	2	23	1	14.7	1.32	2	117	128	61	30	1
1	2	2	1	21	1	15.8	1.97	1	184	94	122	43	1
1	1	1	2	22	1	10.1	1.08	2	138	109	85	31	2
2	2	2	2	26	1	13.7	1.5	2	302	112	227	56	1
1	1	2	1	22	1	10.4	2.03	1	196	272	103	39	1
2	2	1	2	23	1	14.2	1.04	1	253	83	81	56	1
1	2	2	2	20	1	16.6	1.23	1	226	136	164	62	1
2	1	1	2	22	2	7.22	1.09	2	230	149	148	52	2
1	2	2	2	23	1	15.9	2.2	2	238	112	178	68	1
2	1	2	2	22	1	10	1.8	2	246	187	170	40	2
1	2	2	2	21	1	17.5	1.43	1	242	126	186	72	1
1	2	2	2	24	2	7.73	1.06	2	262	164	188	66	2
1	1	2	2	23	2	8.86	1.97	2	266	132	152	52	2
1	2	2	2	24	1	17.7	2.3	1	276	186	178	61	1
1	2	2	2	26	1	14.87	1.3	1	294	163	181	80	1
2	2	2	1	23	1	16.6	1.68	1	180	149	104	46	1
2	1	2	2	22	2	11.2	2.53	1	256	207	172	42	1
1	2	2	2	24	1	1O.3	0.99	1	271	232	158	66	1
2	2	2	2	26	1	18.9	1.07	2	335	385	180	78	1
1	2	1	2	23	1	21.8	2.23	1	198	190	129	31	1
2	1	2	2	21	1	12.8	2.65	1	221	144	162	30	1
1	2	2	2	22	1	22.7	1.9	1	218	113	164	32	1
1	1	1	2	22	1	15.8	2.43	1	206	187	120	48	1

MASTER CHART CONTROLS

Sl.No	AGE	SEX	BMI	T3(ng/dl)	T4(ug/dl)	TSH(uIU/mL)	TC	TG	LDL	HDL
1	26	1	23	88	9.8	1.3	176	97	96	43
2	39	1	22	126	11.2	2.65	152	136	117	60
3	50	1	20	94	7.21	4	179	126	103	46
4	48	1	22	132	6.95	1.53	170	108	88	37
5	44	1	23	112	7.6	2.31	151	137	117	53
6	47	1	22	96	9.7	4.2	139	127	115	38
7	15	1	21	146	9.97	0.89	162	104	107	57
8	50	1	20	135	7.99	4.11	144	113	124	47
9	28	1	21	176	11.51	2.25	179	138	126	49
10	45	1	23	128	6.86	3.53	220	224	150	38
11	22	1	26	89	9	2.12	167	146	120	36
12	33	1	22	148	8.23	1.58	182	140	83	56
13	50	1	19	123	8.63	1.11	194	104	118	62
14	39	1	23	145	7.38	4.18	153	98	78	57
15	49	1	23	88	10.17	3.4	177	138	95	44
16	44	1	20	139	6.82	1.44	142	136	126	48
17	48	1	22	78	9.1	3.99	196	128	98	47
18	39	1	25	143	8.89	4.02	154	114	127	32
19	49	1	21	89	7.34	2.88	132	149	114	44
20	44	1	22	96	9.05	4.3	156	135	105	48
21	47	1	22	112	11.26	2.6	153	105	86	52
22	60	1	21	135	7.02	2.25	171	128	104	54
23	58	1	23	185	9.76	3.6	172	94	124	64
24	30	1	21	183	7.86	3.08	161	129	113	37
25	48	1	20	165	6.51	2.61	148	134	124	49
26	50	1	22	154	11.18	3.64	157	146	127	58
27	52	1	22	98	7.24	4.2	178	101	74	70
28	24	1	22	122	10.4	0.94	162	117	122	62
29	45	1	21	94	5.88	1.36	199	140	127	66
30	56	1	22	86	8.29	2.37	187	99	129	37
31	20	1	21	123	9.56	3.45	148	116	117	71
32	62	1	23	158	5.58	1.36	173	121	94	62
33	54	1	23	160	6.74	1.09	135	126	108	30
34	58	1	27	90	7.32	3.88	164	108	111	53
35	34	1	22	104	11.15	2.84	168	149	75	63
36	63	1	22	128	9.35	4.17	202	164	145	32
37	53	1	20	110	6.37	1.37	160	139	88	46
38	59	1	21	102	8.05	1.45	147	93	92	47
39	55	1	25	128	7.85	2.78	155	125	106	34
40	56	1	22	98	8.26	3.45	165	130	101	68

KEY TO MASTERCHART

Sex

Female 1

Male 2

Symptoms

Weight gain

Present 1

Absent 2

Constipation

Present 1

Absent 2

Cold intolerance

Present 1

Absent 2

Tiredness

Present 1

Absent 2

Depression

Present 1

Absent 2

Musculoskeletal symptoms

Present 1

Absent 2

Menorrhagia

Present 1

Absent 2

Infertility

Present 1

Absent 2

Voice changes

Present 1

Absent 2

Neck swelling

Present 1

Absent 2

Asymptomatic

Yes 1

No 2

Salt intake

Iodised 1

Non iodised 2

PAST HISTORY

Hypertension	Diabetes mellitus	IHD
Present 1	Present 1	Present 1
Absent 2	Absent 2	Absent 2

Thyroidectomy	Hyperthyroidism
Present 1	Present 1
Absent 2	Absent 2

HISTORY OF DRUG INTAKE

1.Lithium 2.Amiodarone 3. Antithyroid drugs 4.Radioiodine 5.Interferon

Yes 1

No 2

SIGNS

Pulse	Blood pressure	Goitre	Dry skin
Normal 1	Normal 1	Yes 1	Yes 1
Bradycardia 2	Hypertension 2	No 2	No 2

Puffy eyes	Delayed relaxation of ankle jerk
Yes 1	Yes 1
No 2	No 2

INVESTIGATIONS

Fasting blood sugar(FBS)

Normal 1

High 2

TPO antibody

Positive 1

Negative 2

Levothyroxine(LT4) treatment

Started 1

Not started 2

APPENDIX III

ETHICAL COMMITTEE APPROVAL

K.Dis.No.4735/E4/1/2008

Government Rajaji Hospital,
Madurai – 625 020.

Date : 11.06.2008

Sub: Establishment – Government Rajaji Hospital, Madurai – Ethical Committee Projects approved approved by the Committee Intimation SentRegarding.

% % % % %

The Ethical Committee of the Government Rajaji Hospital, Madurai was held at 12.30 Noon on 05.06.2008 at the Dean's Chember Government Rajaji Hospital, Madurai and the following Projects were approved unanimously by Committee Members

S.No	Name of the PG	Course	Name of the Project Approved
01	Dr.S.Ramu,,	Gen.Medi	Impact of smoking on glycemic status
02.	Dr.S.Jeyachandran	Gen.Medi	Preval.of peripheral vascular disease in Chronic renal failure.
03.	Dr.K.Preamkumar	Gen.Medi	A Study of Renal Function Abnormalities in Patients with HIV Infection and Aids.
04	Dr.J.Prem Geovanni	Gen.Medi	Serum uric acid as a marker of cornonary artery Disease in type 2 diabetes mellitus patient.
05	Dr.N.Tahasin	Gen.Medi	Evaluation of Chest X – ray features in HIV positive and negative Individuals with sputum positive pulmonary Tuberculosis.
06	Dr.K.Pramodh.	Gen.Med	Clinical profile and lipid abnormalities of Sub clinical Hypothyroidism.
07	Dr.C.Sekar.	Gen.Medi	Chronic renal failure patients admitted in medical wards
08	Dr.G.Ranganathan	Gen.Medi	Evaluation of Postprandial Hypertriglyceridemia as a Risk Factor for Vascular Complication like cardio vascular disease in Type 2 diabetic patients.
09	Dr.D.P.Punitha,	Gen.Medi	Evaluation of Postprandial Hypertriglyceridemia as a risk factor for vascular complication like cardiovascular disease in type 2 diabetic patients.
10	Dr.M.Sampath Kumar	Gen.Medi	Carotid intima media thickness as a merker of coronary artery disease in newly detected type 2 diabetes mellitus patients.

11	Dr.E.Subbiah	Gen.Medi	A study on the prevalence and risk factors associated with peripheral vascular disease in type 2 diabetes.
12	Dr.Annob John.	Gen.Medi	Lipid abnormalities in HIV patients on ART
13	Dr.N.Suresh	Gen.Medi	Dyslipidemia and Hypertension in Obese patients with correlation to BMI
14	Dr.R.Arul	Gen.Medi	Study of Hematologocal profile in rheumatoid arthritis patients.
15	Dr.T.Jamunadevi	Gen.Medi	Hyperamylasemia and acute pancreatitis following organo phosphorus compound poisoning

Please note that the investigator should adhere the following ;

1. She / He should get a detailed informed consent from the patients / participants and maintain Confidentially.
2. She / He should carry out the work without detrimental to regular activities as Well as without extra expenditure to the institution to Government.
3. She / He should inform the Institution Ethical Committee in case of any change Of study procedure site and investigation or guide
4. She / He should not deviate for the area of the work for which applied for Ethical clearance
5. She / He should inform the IEC immediately, in case of any adverse events or Serious adverse reactions.
6. She / He should abide to the rules and regulations of the Institution.
7. She / He should complete the work within the specific period and apply for if any Extension of time is required She should apply for permission again and do the work.
8. She / He should submit the summay of the work to the Ethical Committee on Completion of the work.
9. She / He should not claim any funds from the Institution while doing the Work or on completion.
10. She / He should understand that the members of IEC have the right to monitor the Work with prior Intimation.

DEAN/ CHAIRMAN,
ETHICAL COMMITTEE,
GOVERNMENT RAJAJI HOSPITAL,
MADURAI.

To
The above Post Graduates though the Head of the Departments Concerned.

forwarded
14/6/08

PROFESSOR AND HEAD
DEPARTMENT OF MEDICINE
MADURAI MEDICAL COLLEGE
MADURAI-625 020.

APPENDIX IV

ABBREVIATIONS

BMI - Body mass index

BP- Blood pressure

CHD - Coronary heart disease

DRAJ- Delayed relaxation of ankle jerk

FBS –Fasting blood sugar

HDL - High density lipoprotein

I Q - Intelligence quotient

LDL - Low density lipoprotein

PAF - Platelet activating factor

PAF- AH- Platelet activating factor acetyl hydrolase

RAI- Radio active iodine

T3 - Total triiodothyronine

T4 – Total thyroxine

fT4- Free thyroxine

TSH – Thyroid stimulating hormone

TRH – Thyrotropin releasing hormone

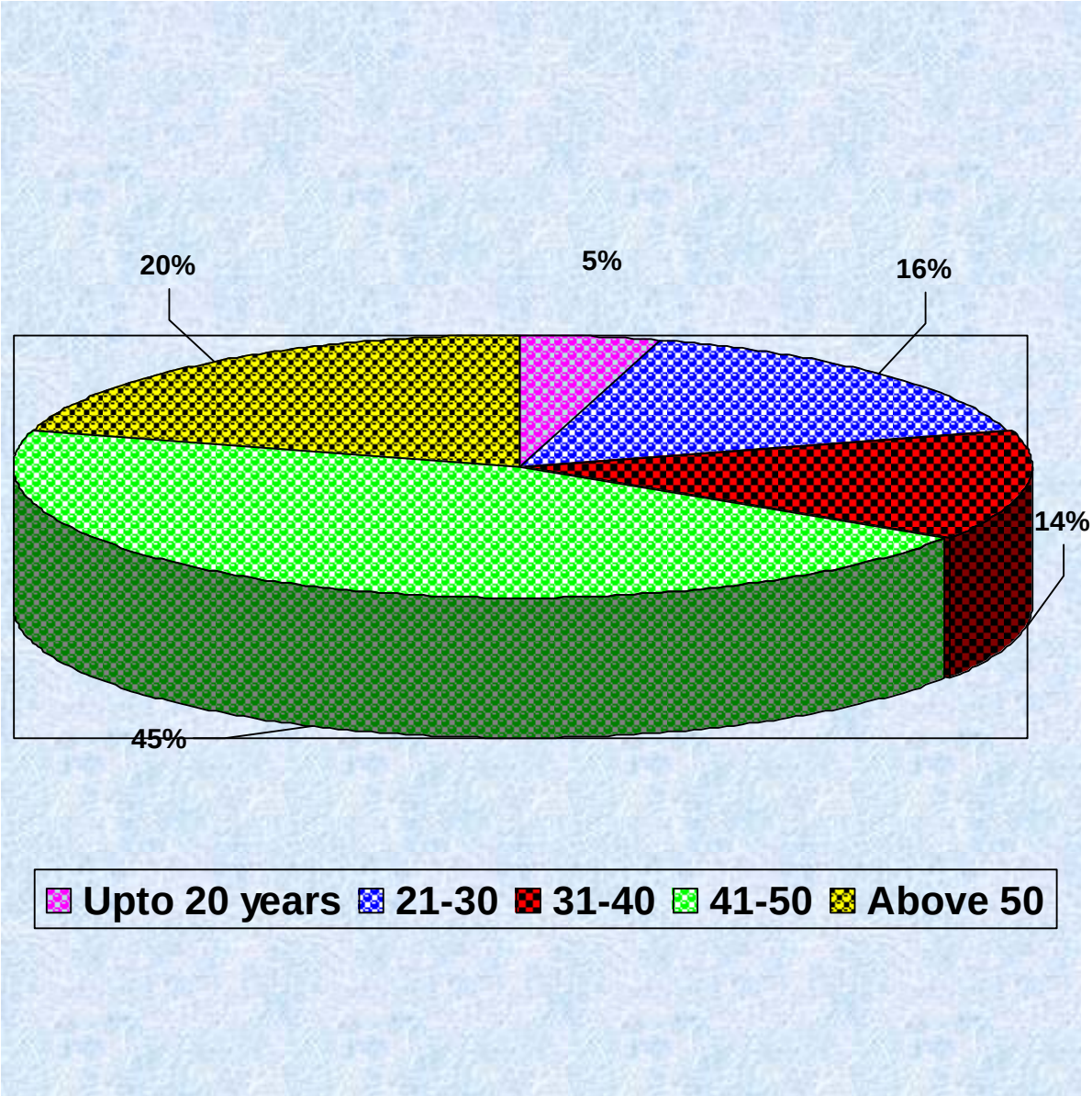
TPO – Thyroid peroxidase

TC – Total cholesterol

TG - Triglycerides

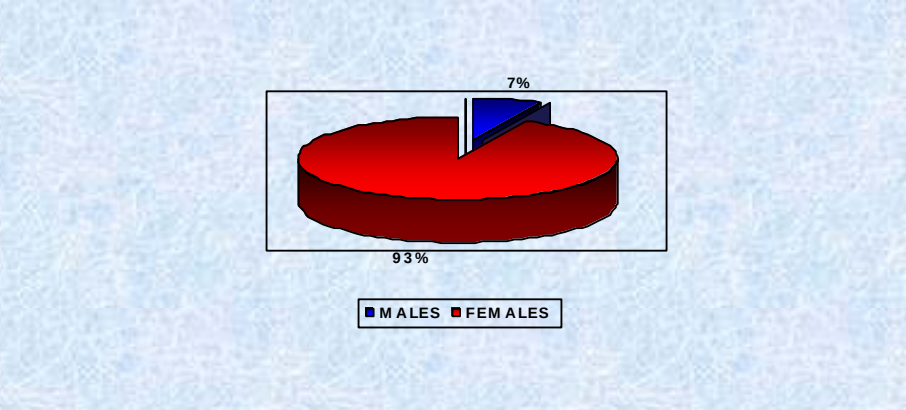
AGE DISTRIBUTION

Fig 2



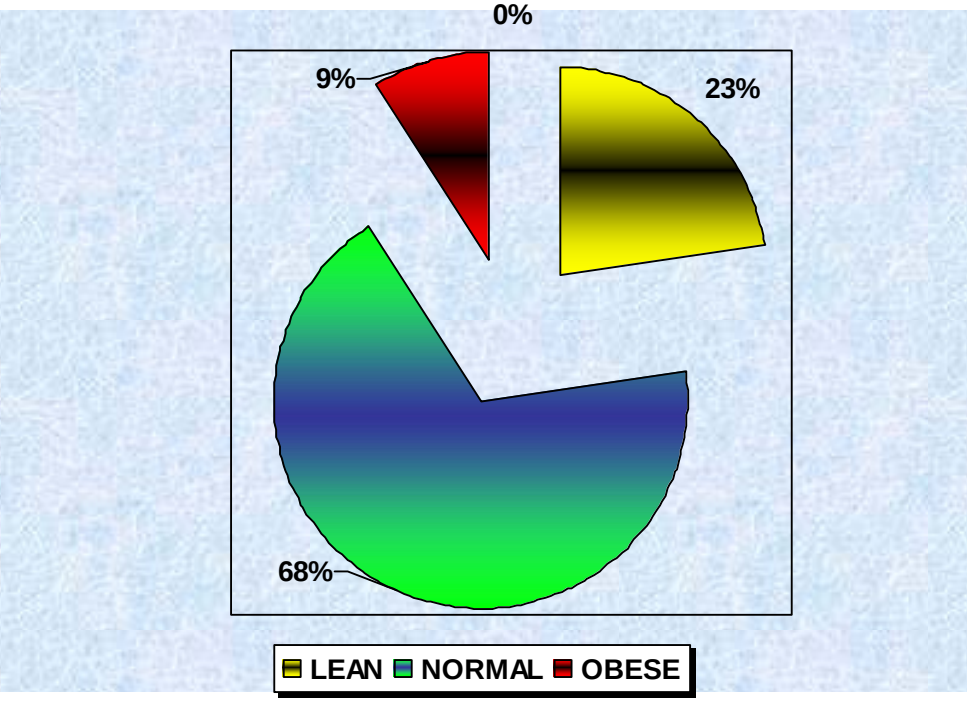
SEX DISTRIBUTION

Fig 3



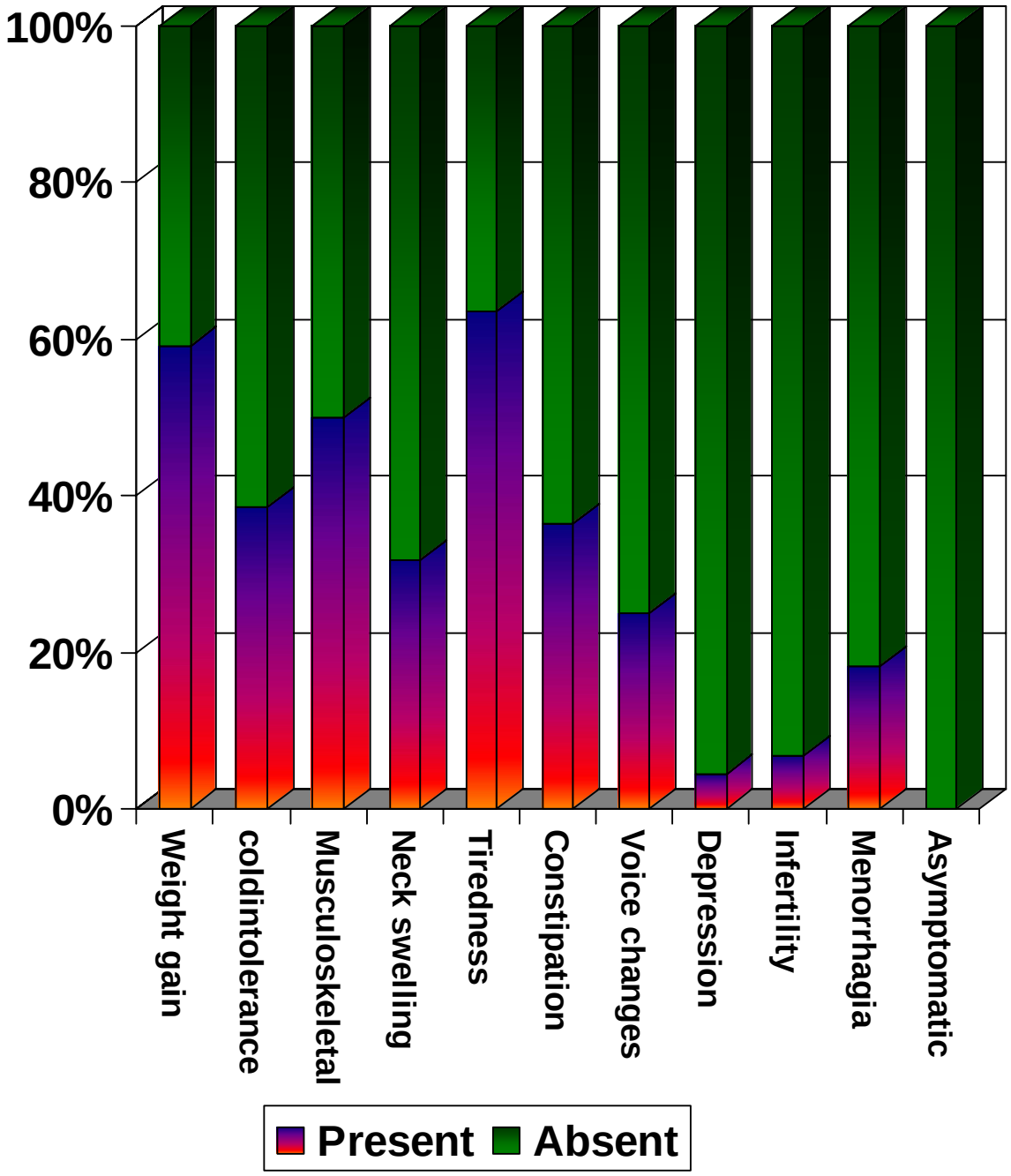
B M I

Fig 4



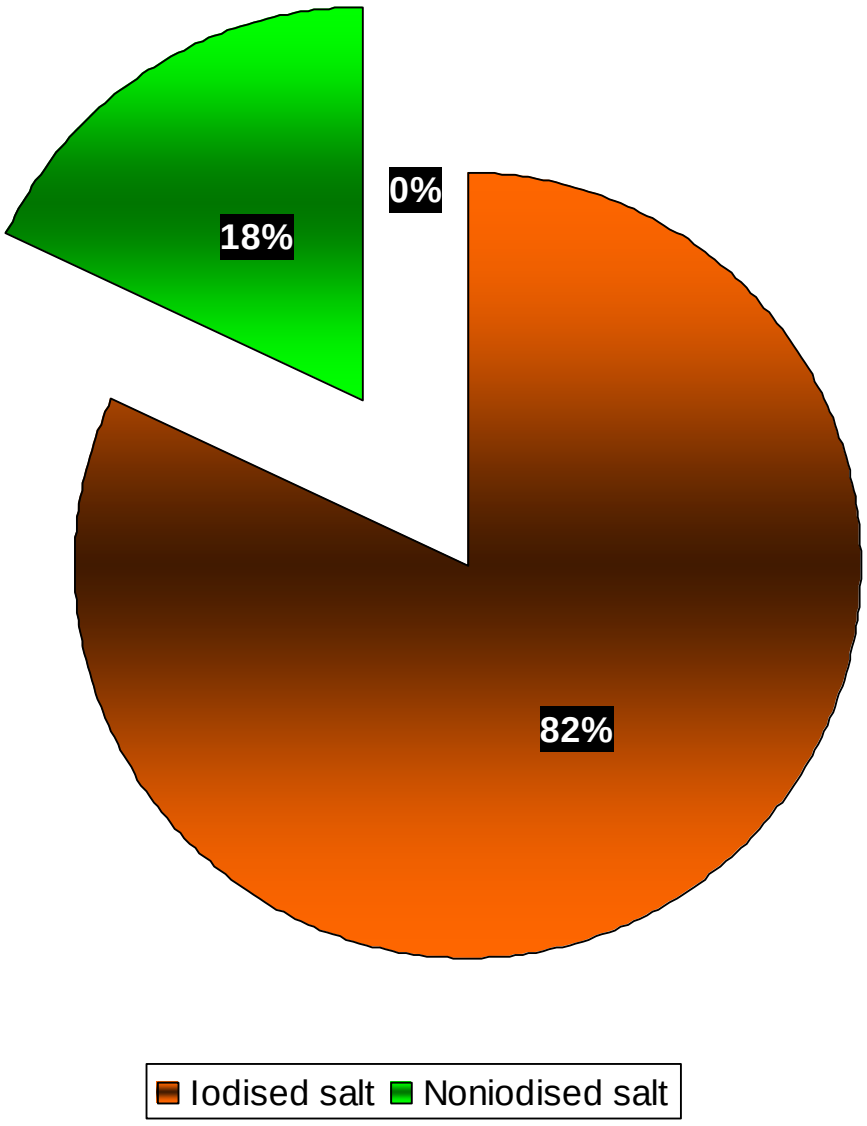
SYMPTOMS

Fig 5



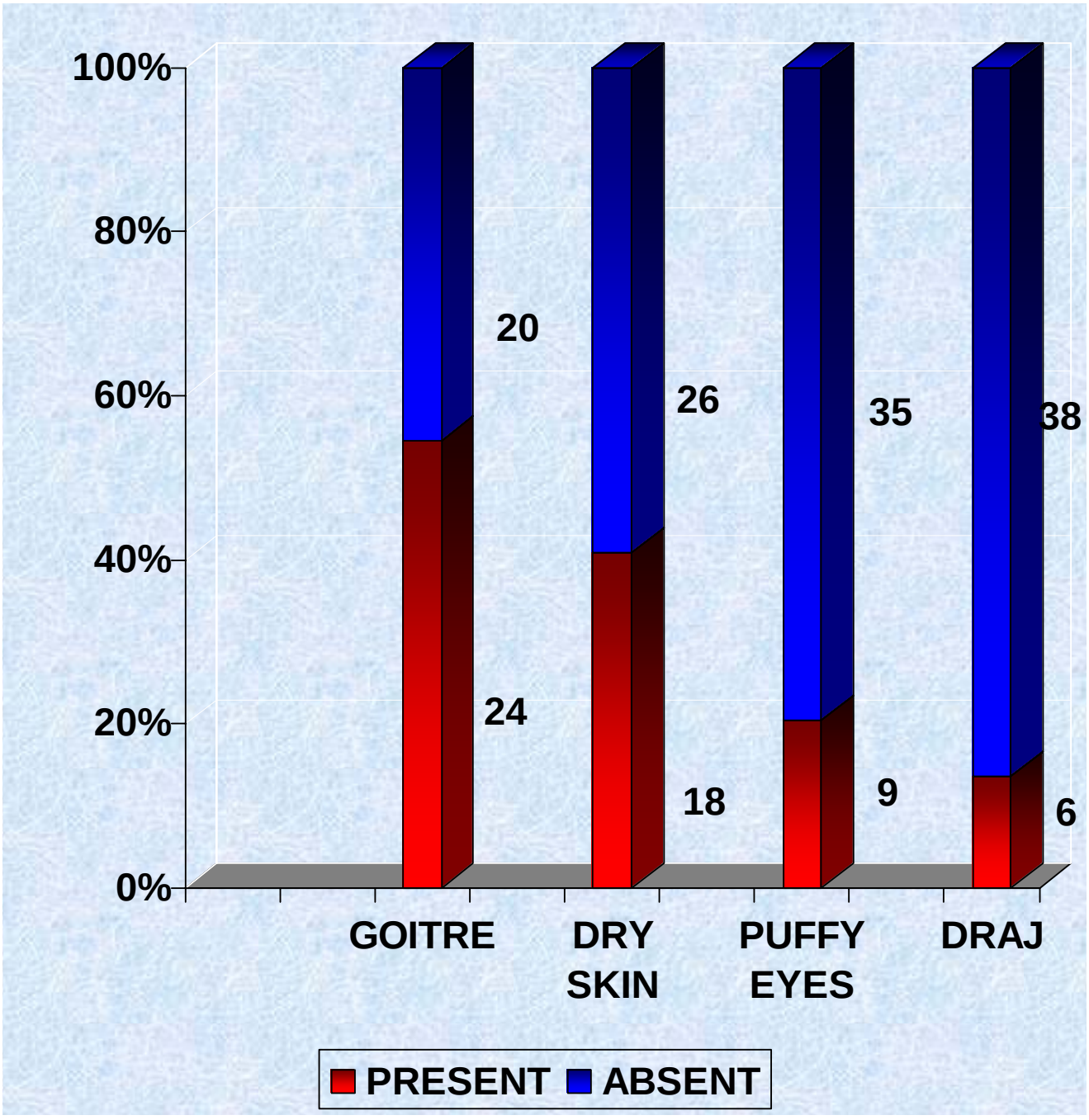
SALT INTAKE

Fig 6



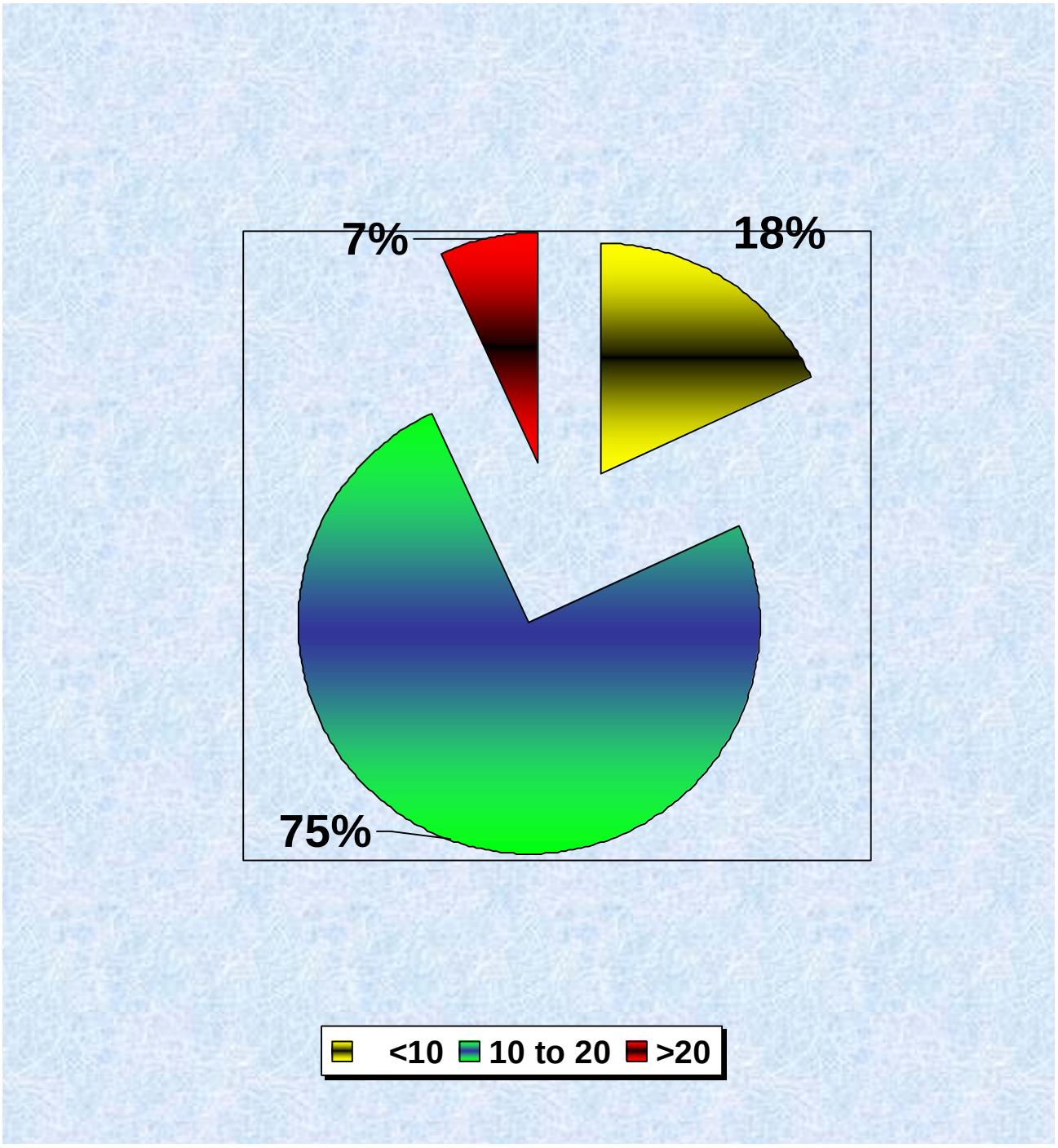
SIGNS ON CLINICAL EXAMINATION

Fig 7



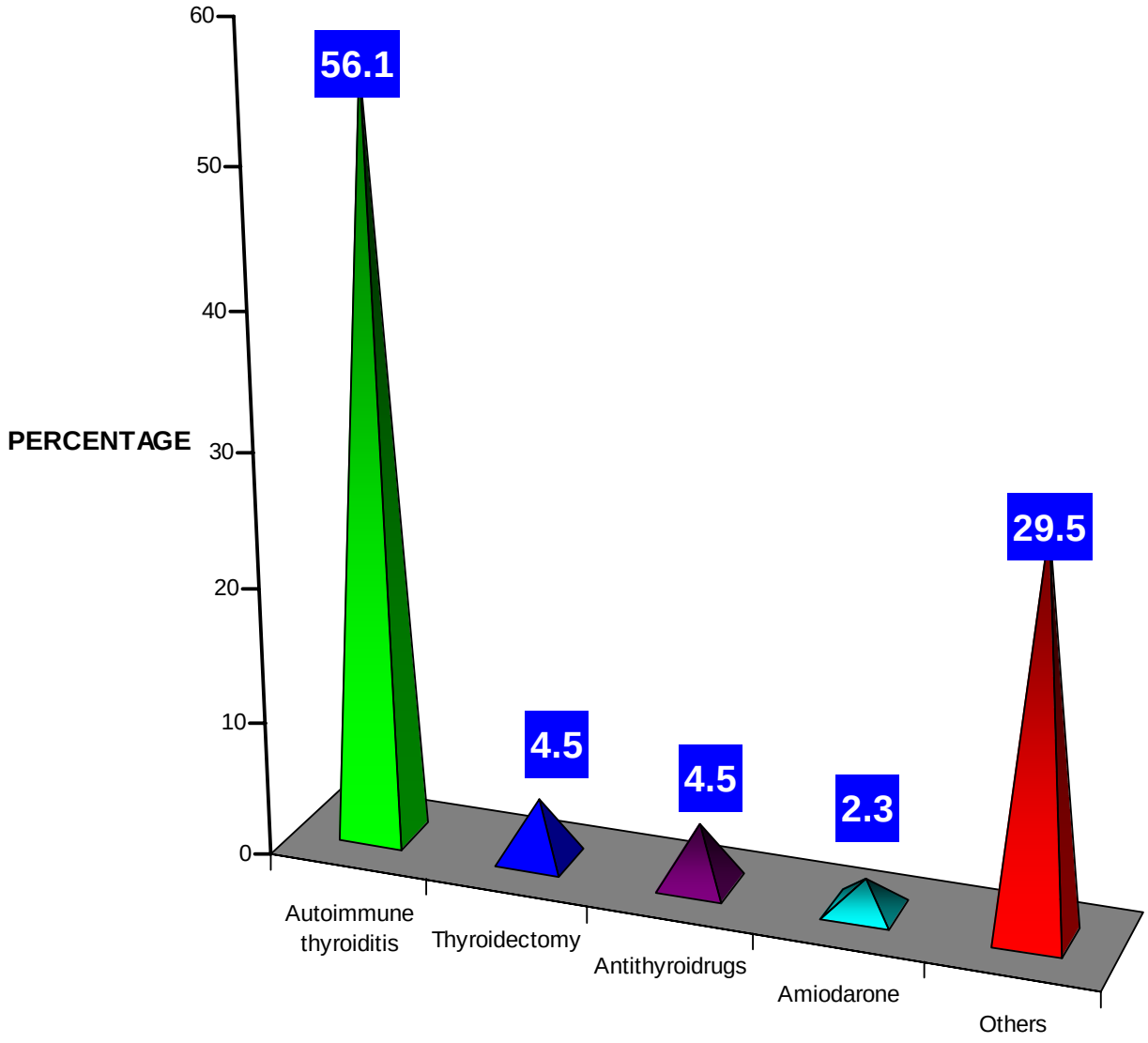
TSH DISTRIBUTION

Fig 8



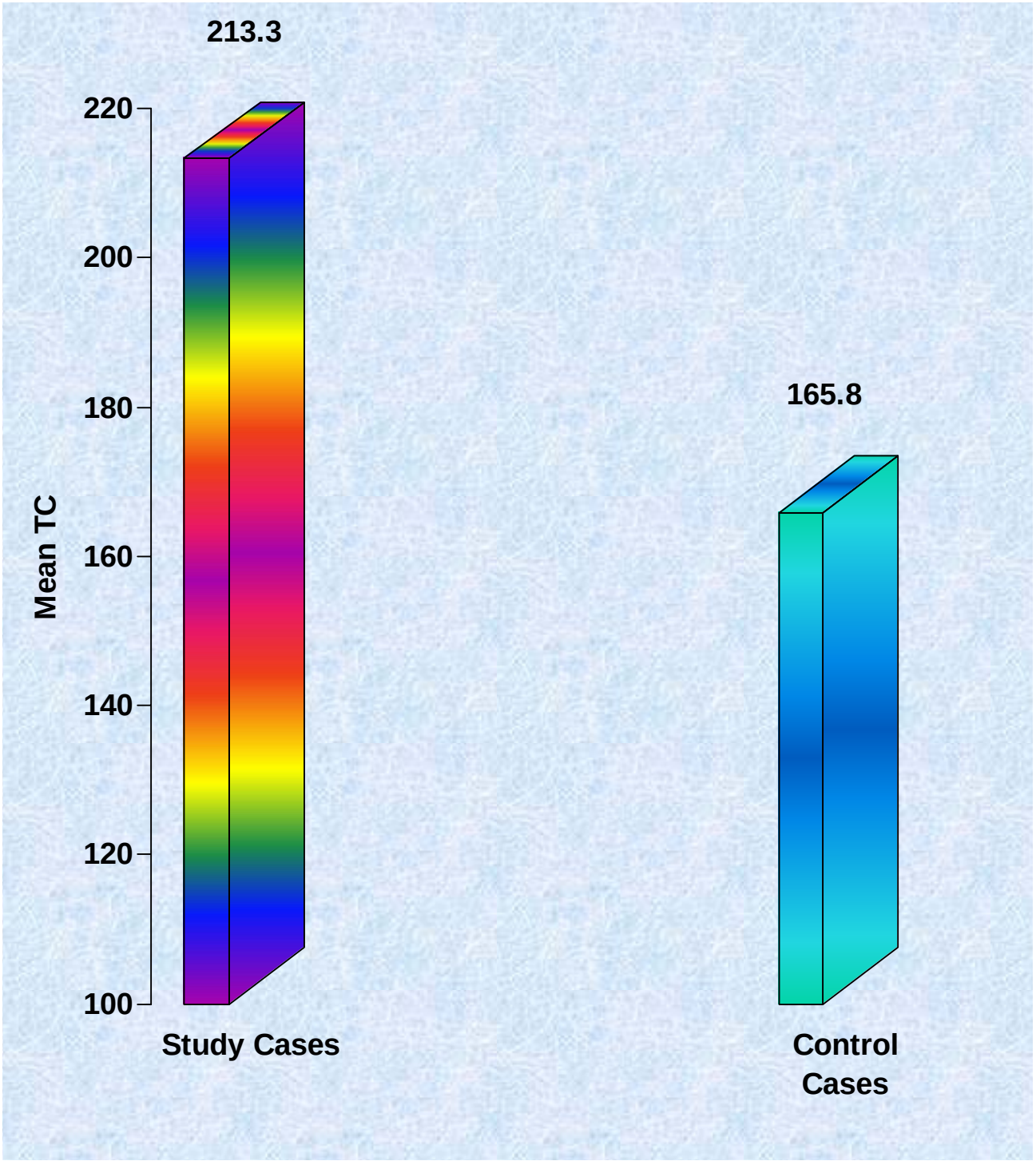
ETIOLOGIES OF SUBCLINICAL HYPOTHYROIDISM

Fig 9



TOTAL CHOLESTEROL

Fig 10



LDL CHOLESTEROL

Fig 11